ELSEVIER
SAUNDERS

RHEUMATIC DISEASE CLINICS OF NORTH AMERICA

theclinics.com

Preface

Steven E. Carsons, MD
Guest Editor

Sjögren's syndrome (SS) is atypical among the major autoimmune rheumatic diseases encountered by the rheumatologist. The predominance of ocular, oral mucosal, and exocrine gland pathology accompanied by the copresence of multiple organ-specific autoimmune disorders results in a somewhat unfamiliar diagnostic and therapeutic landscape. The lack of universally accepted diagnostic, classification, and outcome criteria, as well as the need for close collaboration with ophthalmologic, dental, and otolaryngologic subspecialists for optimal patient management, all contribute to challenges in management. Nevertheless, SS affords rheumatologists and immunologists an opportunity to understand the pathogenesis, long-term evolution, and outcome of an autoimmune disease that possesses both organ-specific and systemic features. In addition, the frequent co-occurrence of SS with other major rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosis, and scleroderma, affords a unique insight into genetic, environmental, and biologic factors controlling the expression of autoimmune phenotypes among patients who have connective tissue disorders. The striking association between primary SS and non-Hodgkin's lymphoma provides valuable insight into the relationships among autoimmunity, immunogenetics, and malignancy. Finally, significant inroads are being made with regard to therapy for the glandular and systemic manifestations of SS. For all of these reasons, basic and clinical, investigation into SS has dramatically increased over the past decade, as demonstrated by manuscripts submitted to rheumatology journals and abstracts presented at the American College of Rheumatology and other scientific meetings. This issue is intended to reflect a cross-section of advances made in these key areas.

Delaleu and colleagues review advances in our understanding of the immunopathogenesis of SS. Ability to perform multiple genomic and proteomic arrays has identified signatures of specific cytokine-activated genes. The authors hypothesize that the activation of different immune compartments may correlate with diverse functional outcomes in SS, an important clue for the design of therapeutic approaches. Interaction of specific major histocompatibility complex (MHC) haplotypes with the environment has long been suspected to be significant in the pathogenesis of SS. Cobb and colleagues provide a comprehensive look at MHC and non-MHC genes associated with populations having an elevated risk for the development of SS. These genes

Rheum Dis Clin N Am 34 (2008) xiii–xv
doi:10.1016/j.rdc.2008.10.001 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

may also serve as potential targets for interruption of immunopathogenic pathways. Ongoing development of high throughput DNA analytic methodology continues to provide rapid advances in the identification of relevant genes. Viral agents have been the focus of investigation as environmental etiologic agents for SS for over 50 years. Epidemiologic data and similarities in clinical phenotype suggest roles for several viruses in the causation of SS-like syndromes. These viruses include Epstein-Barr virus, human T cell lymphotropic virus-1, HIV, and hepatitis C virus. Ramos-Casals, Muñoz, and Zerón provide a detailed analysis of SS associated with hepatitis C virus infection and discuss immunopathologic scenarios and classification schemes.

Newly evolving concepts of primary SS have resulted in its characterization as a systemic disease displaying significant extraglandular manifestations. The nervous system has emerged not only as a prominent target of inflammation in SS, but also as an important physiologic regulator of lacrimal and salivary secretion. Segal, Carpenter, and Walk provide an elegant synthesis of the role of the nervous system in both the pathogenesis of SS and the expression of the clinical phenotype. As a continuum of the epithelial organs of the oro-nasopharynx, the upper and lower airways frequently become involved in SS. Parke reviews airway manifestations of SS secondary both to sicca and to autoimmune inflammatory mechanisms. Diagnosis and management of lymphoma presents one of the greatest challenges to rheumatologists caring for patients who have SS. Voulgarelis and Moutsopoulos update data describing the relative risk for lymphoma in primary SS. The authors also describe novel paradigms for B-cell lymphoma classification in the context of SS and provide a framework for management.

In addition to presenting as primary or secondary disease, SS can occur in association with organ-specific autoimmune diseases, as well as in overlap scenarios with the major connective tissue diseases. Theander and Jacobsson review the association of SS with other autoimmune diseases in the context of the American European Consensus Criteria (AECC) and proposed outcome measures for SS. Efforts continue to develop outcome measures for SS to better understand the natural history, prognosis, functional consequences, and response to experimental therapeutics. Bowman explores the role of patient-reported outcome measures, with a particular emphasis on fatigue. Vitali describes the efforts of Italian and other European investigators to develop activity and damage measures. Although much recent activity has occurred with regard to investigations exploring the role of multiple imaging modalities for the diagnosis, classification, and functional assessment of SS, nuclear scintography remains the only noninvasive imaging modality included in the AECC. Vivino and Hermann describe issues involved in proper performance and interpretation of salivary scintography.

Although rheumatologists routinely collaborate with ophthalmologists in the management of the ocular manifestation of SS, a working knowledge of advances in ophthalmologic care is essential for counseling patients and monitoring therapy. Foulks reviews advances in the pathophysiology of dry eye and the effect of understanding pathophysiologic mechanisms on the development of newer topical agents for xerophthalmia. Similarly, Wu reviews the effects of hyposalivation on oral mucosal pathology and discusses important aspects of dental management in SS patients, including prophylactic measures, use of salivary substitutes, and treatment of oral superinfection.

Effective disease modifying therapy remains an elusive goal in SS. The guest editor reviews data from studies assessing a variety of approaches to disease modification in primary SS. Issues impacting the design and performance of clinical trials in primary SS are highlighted.

In the final article, Mariette reviews current data and discusses future approaches to therapeutic B-cell modulation, the most recent approach with potential for controlling glandular and extraglandular disease and for lymphoma-risk modification in SS.

It is the hope of the guest editor that the contributions published in this issue stimulate enhanced efforts at achieving optimal clinical care for SS patients and new approaches to investigations into the etiology, clinical course, and treatment of SS.

Steven E. Carsons, MD
Division of Rheumatology, Allergy, and Immunology
Winthrop University Hospital
120 Mineola Boulevard, Suite 410
Mineola, NY 11501, USA

E-mail address:
scarsons@winthrop.org

New Concepts in the Pathogenesis of Sjögren's Syndrome

Nicolas Delaleu, PhD[a], Malin V. Jonsson, DMD, PhD[a,b], Silke Appel, PhD[a], Roland Jonsson, DMD PhD[a,c,d,*]

KEYWORDS

• Sjögren's syndrome • Etiology • Pathogenesis • IFN-α • B cells • Biomarkers

Sjögren's syndrome (SS) is a chronic autoimmune disease affecting mainly the exocrine glands. Nearly all patients complain of a persistent feeling of dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca).[1,2] The subjective symptoms can be confirmed by objective tests, showing significant functional impairment in saliva secretion capacity and tear production. Histologic evaluation of the salivary and lacrimal glands show large and persistent infiltrates of mononuclear cells within the glandular tissue. Beside lymphocytic infiltration, acinar epithelial cell atrophy and progressing fibrosis can be observed within glands from patients who have SS. Traditionally, loss of secretory capacity, degree of lymphoid infiltration and production of specific autoantibodies were anticipated to correlate with each other and indicate disease state and disease severity.[1,2] The correctness of this assumption is, however, difficult to prove and may not apply to all patients. Processes disturbing the physiologic cascade of saliva production and secretion are proposed as a possible explanation for this phenomenon.[3]

Financial support: European Union (BMH4-CT96-0595, BMH4-CT98-3489, QLK2-1999-51079, QLK2-CT-2001-30115, MEST-CT-2004-514483, and MEIF-CT-2007-041083), Norwegian Research Council, Strategic Research Program at Helse Bergen, Western Norway Regional Health Authority, Norwegian Cancer Society, and Broegelmann Foundation.

[a] Broegelmann Research Laboratory, The Gade Institute, University of Bergen, Haukelandsveien 28, Bergen 5021, Norway
[b] Section for Rheumatology, Institute of Medicine, University of Bergen, Jonas Liesvei 65, Bergen 5021, Norway
[c] Department of Rheumatology, Haukeland University Hospital, Jonas Liesvei 65, Bergen 5021, Norway
[d] Department of Otolaryngology, Head and Neck Surgery, Haukeland University Hospital, Jonas Liesvei 65, Bergen 5021, Norway
* Corresponding author. The Gade Institute, Research Laboratory, University of Bergen, Armauer Hansen Building, Haukelandsveien 28, NO-5021, Bergen, Norway.
E-mail address: roland.jonsson@gades.uib.no (R. Jonsson).

Rheum Dis Clin N Am 34 (2008) 833–845
doi:10.1016/j.rdc.2008.08.004 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

Affecting approximately 0.3% to 0.6% of the total population, SS is considered one of the most common autoimmune diseases and with a ratio of 9:1 exhibits one of the highest female-to-male ratios among autoimmune diseases. Beside sicca symptoms, pain and especially fatigue contribute to the significant decrease in quality of life and psychologic status in patients who have SS compared with the general population.[4] The disease may extend from an autoimmune exocrinopathy to the manifestation of diverse extraglandular symptoms, such as involvement of the musculoskeletal, pulmonary, gastrointestinal, hepatobiliary, hematologic, vascular, dermatologic, renal, and nervous systems.[1] SS may occur alone, defined as primary SS (pSS), or in association with another defined autoimmune disease (eg, systemic lupus erythematosus [SLE], rheumatoid arthritis [RA], or scleroderma) and then is termed secondary SS.[1]

In contrast to SLE where increased mortality, especially in connection with cardiovascular disease, has been reported, the overall mortality in SS is comparable to the mortality rate in the normal population.[5] Nevertheless, excess mortality related to the increase in risk for developing non-Hodgkin's lymphoma has been reported.[5] The previous estimate of a 40-fold increased risk for lymphoma development was, however, reconsidered after a large registry-linked study proposed the increase as approximately 16-fold.[6]

This review attempts to cover the latest concepts on the etiology and recently proposed disease mechanisms involved in the pathology of SS.

ETIOLOGY

As is true for most autoimmune diseases, the etiology of SS is at present unknown. Environmental factors in concert with an appropriate genetic background are believed to be capable of triggering SS. The enigma of the initiating event leading to the accumulation of mononuclear cells in the exocrine glands characteristic of SS has not yet been solved, however. A viral infection targeting the salivary glands has been proposed as the origin of such inflammation.[7–9] Subsequently, the immune attack, initially serving the purpose of host-defense, might through molecular mimicry be converted into a pathologic immune reaction directly targeting self-determinants.

Another concept follows the perception that autoimmune diseases arise from a divergence between the actual tissue state and the immune system's perception of the situation.[10] Autoimmune diseases, in such a case, would be marked by insufficient anti-autoimmune regulation against key self-molecules.

As is true for other autoimmune diseases, a genetic predisposition for SS seems to exist, based on the accumulation of SS in certain families and among twins.[11] Recently, a variant of the minor histocompatibility antigen, HA-1, has been associated with reduced risk for pSS.[12] However, no association with polymorphisms in Fas and FasL,[13] interleukin (IL)—10, tumor necrosis factor α (TNF-α), IL-1 receptor antagonist,[14] cytotoxic T-lymphocyte–associated protein 4,[15] TNF-α receptor 2,[16] and chemokine (C-C motif) receptor 7[17] was observed (for a more complete discussion about genes potentially associated with SS, see the article elsewhere in this issue).

The infectious agents that have received most attention in the field of SS are Epstein-Barr virus,[7] human T-cell leukemia virus 1,[8] and hepatitis C.[9] Association with all these candidates has remained, however, weak. A more recent study in a Greek population[18] identified a coxsackievirus as a potential agent, which could be involved in the induction or maintenance of SS. These results could not be validated, however, in a French patient cohort.[19] Microarray-based investigations of the salivary gland transcriptome in patients who have SS[20] and in congenic mouse models for SS[21,22] showed activation of type I and type II interferon (IFN)-related genes. Such

activation, potentially originating from a viral infection, may be perpetuated by RNA-containing immune complexes, in turn activating plasmacytoid dendritic cells (DCs) to sustain IFN-α production at the tissue level.[23] The finding that U1 small nuclear RNA and hY1RNA, the latter known to associate with SS-A/Ro, have the capacity to induce IFN-α further argues for the existence of this mechanism.[24]

Female predominance and the late onset of SS directed attention toward sex hormones and their potential role in the etiology of SS. In general, androgenic hormones have been considered to protect from autoimmunity, and it has been proposed that women who have SS are androgen deficient.[25] Although neither estrogen receptor α– nor estrogen receptor β–deficient mice develop SS, another model for estrogen deficiency, the aromatase-knockout mouse, develops a lymphoproliferative autoimmune disease resembling SS, paralleled by B-cell infiltration of the kidneys and enlargement of the spleen.[26] Microchimerism of fetal cells also may play a role in generating an autoimmune state in women who have been pregnant.[27]

Experiments in nonobese diabetic (NOD) scid[28] and Id3$^{-/-}$[29] mice support a possible relationship between defective organ development and initiation of a pathologic immune reaction targeting the salivary glands. In the latter model, depletion of B cells ameliorated the SS-related symptoms.[30]

TOLERANCE AND IMMUNE REGULATION BY DENDRITIC CELLS

DCs are the most potent antigen-presenting cells of the immune system.[31] DCs are critical for the induction not only of central but also of peripheral tolerance. DCs present self-antigens to T cells leading to anergy or deletion in case of autoreactivity.[32,33] Moreover, DCs are important for the induction of regulatory T-cells (Tregs) that act as suppressor cells and help in the maintenance of tolerance.[34,35] Induction of autoimmune diseases by DCs has been demonstrated in model systems.[36,37] Moreover, a recent study showed that mice with apoptosis-defective DCs display classical signs of autoimmunity, including antinuclear antibody production.[38] This group further demonstrated that deficiency of the pro-apoptotic BH3-only protein, Bcl-2 interacting mediator of cell death (Bim), causes overstimulation of T cells and autoimmunity in DCs.[39] As an activated type I interferon signature has been observed in salivary glands of patients who have SS,[23,40] more attention has been given to plasmacytoid DCs,[41] the main type I interferon–producing cells. They have been found in salivary glands of SS patients but not in controls,[23,40] underscoring the hypothesis that these cells might play an important role in the etiology of SS.

THE LYMPHOEPITHELIAL LESION AND LYMPHOID NEOGENESIS

Leukocytes circulate in the periphery and invade target tissues in response to an infection or trauma. Most likely, the presence of focal mononuclear cell infiltrates in exocrine tissues is a result of quantitative changes in molecules involved in attraction and retention of inflammatory cells within the target tissue.[42,43] The accumulation of inflammatory cells also may be favored by an environment promoting cell proliferation and reducing cell death of specific cell subsets.[44] Leukocyte chemoattraction and organization is mediated by chemokines, but despite their uncontested potential as candidates for therapeutic intervention and their involvement in angiogenesis, fibrosis, and malignancy,[45] they remain rather poorly examined in the context of SS.[42,46,47,48] Angiogenesis or neovascularization, responsible for paving the path for increased cell migration, until now has received little attention in the field of SS.[42,48]

The focal inflammation in the exocrine glands consists mainly of T cells and B cells with fewer DCs[40] and macrophages (**Fig. 1**).[49,50] Serum levels of E-cadherin, an

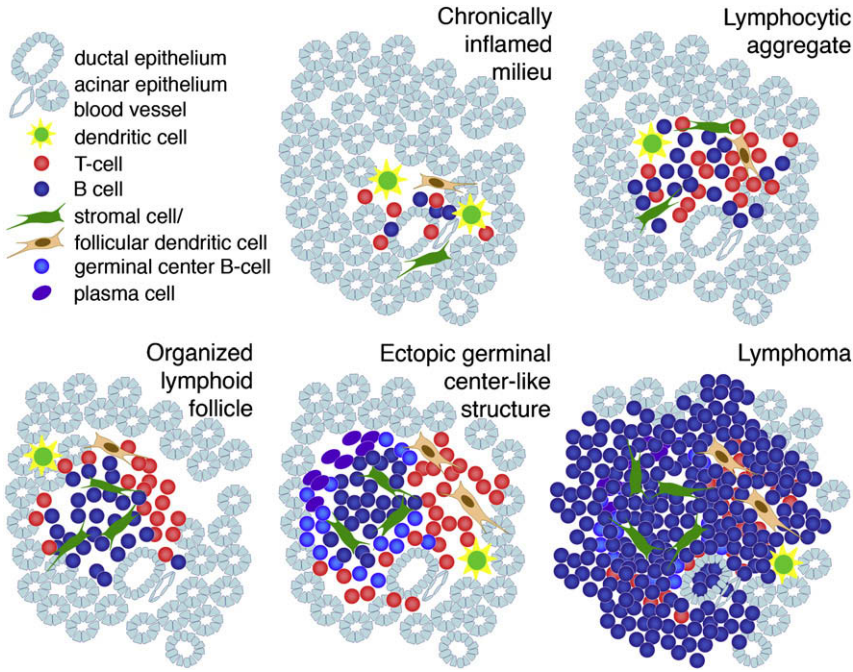

Fig. 1. Hypothetical steps leading to the formation of a germinal center in exocrine tissues. Activated T cells, B cells, and DCs frequently are observed in the salivary and lacrimal glands in SS and preferentially accumulate around blood vessels and ductal epithelial structures. Upon entering the target tissue, activated lymphocytes may induce a change of stromal cells into follicular DCs (FDCs) producing specific chemokines, leading to the attraction of more B and T cells. Organized follicles composed of B cells and a network of functionally mature FDCs form GC-like follicles. T cells and plasma cells are present at the periphery of the follicle. This milieu eventually may promote neoplastic transformation.

adhesion molecule related to epithelial cells, was found to be increased in SS, indicating the close interaction between epithelial cells and lymphocytic organization.[49] Furthermore, epithelial cells of patients who have SS have been reported to express Toll-like receptors, which argues for a role for these cells in perpetuating the disease[51,52] perhaps via binding viral RNAs. The role of Tregs in the progression of SS still is elusive.[53–55] Nonetheless, the SS-like disease course in NOD mice deficient for E2f1, which results in a profound decrease in Tregs, is accelerated and aggravated.[56] Hence, strengthening regulatory mechanisms should be paralleled by restoration of immunologic tolerance[48,57,58] in SS, without resorting to long-term generalized immunosuppression.[59]

Histologic and immunohistologic investigations of minor salivary gland specimens have identified germinal center (GC)-like structures in approximately every fourth patient who has pSS (see **Fig. 1**).[60] Generation of a patient's individual cytokine and chemokine profile, using a bead-based multiplex immunoassay, revealed serum biomarker signatures potentially indicative of the presence of GC-like structures in the salivary glands.[61] Among 25 biomarkers, discriminant function analysis identified B-cell activating factor (BAFF), chemokine (C-C motif) ligand 11, and IFN-γ levels to discriminate best between patients who have and who did not have GC-like structure formation.[61]

Ectopic GC-like structures also are associated with a higher degree of glandular inflammation and coincide with elevated titers of rheumatoid factor, anti-Ro/SSA, and anti-La/SSB and increased IgG levels.[60,62] The formation of ectopic GC-like follicles in nonlymphoid organs, also known as tertiary lymphoid tissue, may participate in the progression of SS and indicate a more severe disease phenotype. Furthermore, GC-like structures have been associated with the occurrence of lymphoproliferative disorders in SS (see **Fig. 1**).[63] Similar signs of ectopic lymphoid tissue formation and lymphoid neogenesis also occur in RA synovia,[64] in the thyroid gland of Hashimoto's thyroiditis,[65] and chronic infectious reactions triggered by, for example, *Helicobacter pylori* in the gut mucosa.[66]

CYTOKINE RESEARCH AND BIOMARKER DISCOVERY

Cytokines are a diverse group of soluble proteins and peptides, which act as humoral regulators at nano- and picomolar concentrations. Under normal and pathologic conditions they critically modulate the functional activities of individual cells and tissues, thus representing potential drug targets. The therapeutic impact of agents neutralizing the pro-inflammatory cytokine, TNF-α, in patients who have RA was impressive,[67] proving the principle of cytokine inhibition therapy for autoimmune rheumatic diseases. The use of TNF-α antagonists in SS was discontinued, however, because promising initial results could not be confirmed.[68]

Cytokine profiles have been studied in blood and salivary gland tissues from patients who have SS[61,69,70] and in mouse models for SS.[42,71,73] Because cytokines are characterized by redundancy, pleiotropism, synergism, and antagonism, the interpretation of these results often is challenging. Applying the by now expanded concept of Th1/Th2 cytokines and autoimmunity, it has been postulated that Th2 cytokines may be predominant in an early phase of SS, whereas Th1 cytokines are associated with a later stage of the disease.[72] Alternatively, studies in NOD mice revealed that the decrease in salivary flow, which is believed to follow the emergence of glandular inflammation,[73] may be associated with Th2 cytokines.[74,75] In NOD mice, commonly used as a model to study experimental SS, transition between the preclinical and overt disease state, manifested by the onset of hyposalivation, seems dependent on an intact signal transducer and activator of transcription 6 (STAT6) pathway.[76]

Revision of the Th1/Th2 paradigm has resulted from the identification of a helper T-cell subset, termed *Th17*, which produces IL-17 (IL-17A), IL-17F, and IL-22.[76] A major role of IL-17 has been described for various models of immune-mediated tissue injury associated with several autoimmune diseases (eg, RA).[77] Recent results suggest that the TH17/IL-23 system is activated in SS patients and C57BL/6.NOD-Aec1Aec2 mice during the overt disease state. Functional associations between IL-17/IL-23 expression and specific clinical manifestations have, however, not yet been identified.[78]

A study, investigating a total of 162 potential biomarkers in serum and saliva and their association with specific SS-related autoimmune manifestations, concluded that based on correlation networks, processes related to the adaptive immune system promote SS with strong involvement of Th2-related proteins.[42] These proteins also demonstrated a strong association with hyposalivation (**Fig. 2**). Furthermore, autoimmune manifestations of SS were highly independent of each other and most likely are associated with different immunologic processes (see **Fig. 2**).[42]

Because of its ease of collection and noninvasive method of collection, several research groups have revisited saliva as an attractive biofluid for biomarker research in SS. Biomarker signatures in saliva may reflect local disease independently of

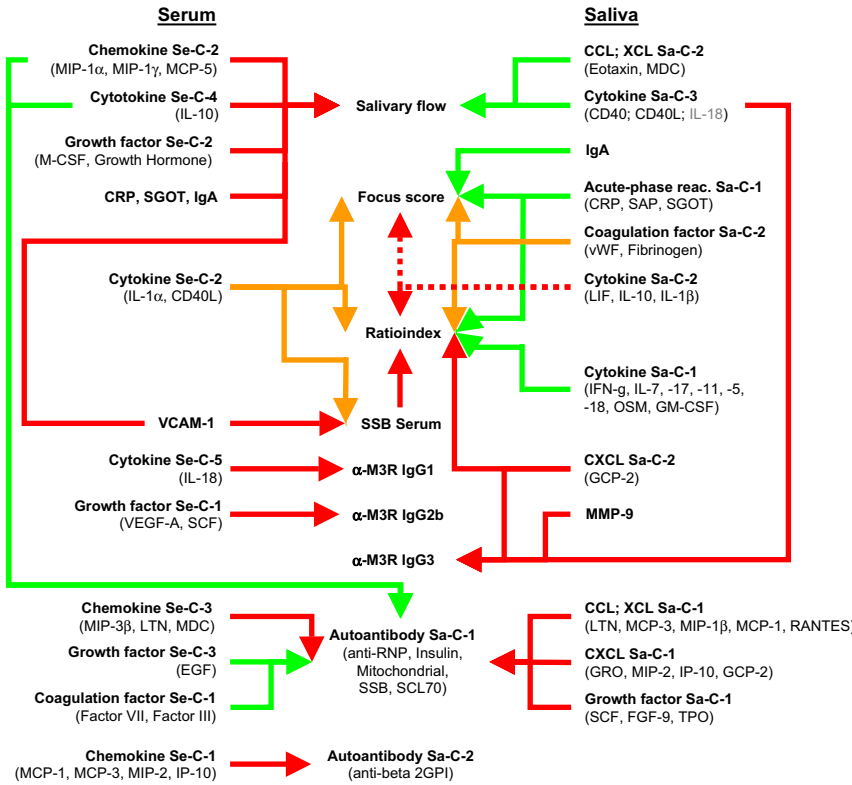

Fig. 2. Correlation network of biomarkers and autoimmune manifestations in a model for experimental SS. Model of principal component associations (defining variables are given in parentheses) and selected original variables with autoimmune manifestations of SS: red arrows mark significant positive correlations and green arrows significant negative correlations. Orange arrows represent significant associations of components with significant positive and negative loadings. Dotted lines and gray lettering mark borderline significances. All data were acquired using a bead-based multiplex immunoassay. (*From* Delaleu N., Immervoll H., Cornelius J., et al. Biomarker profiles in serum and saliva of experimental Sjögren's syndrome—associations with specific autoimmune manifestations. Arthritis Res Ther 2008;10(1):R22; with permission.)

inflammatory systemic disease.[42] Improving patient classification, possibly of the basis of specific biomarkers,[79] is considered an important matter in SS research, as SS largely is diagnosed at a late stage, when glandular dysfunction and symptoms of fatigue already severely affect a patient's overall life quality.[4]

Once validated, appropriate biomarkers could provide physicians with useful information about disease risk, disease state, and progression and allow for close follow-up of responses to treatment intervention. Biomarker identification, using 2-D gel electrophoresis combined with mass spectrometry, has identified 42 proteins, which display significant alteration when pooled saliva from patients who have SS is compared with that from healthy controls.[80] Global mRNA expression conducted in parallel revealed poor correlation between levels of transcripts and protein quantities, pointing out potential limitations of studies that evaluate mRNA only. Technology and techniques for quantitative mass spectrometry are evolving at a fast pace, allowing for

identification of peptides, which could be of interest for preliminary validation steps.[81] Nonetheless, identification of immunologic regulators, operating at nano- to picomolar concentrations, still constitutes a great challenge, as abundant proteins may mask immunologic modulators in the biofluid of interest.[81] The gold standard technique for quantitative measurements of immunoreactants still is immunoassay, as a result of the unmatched sensitivity provided by antibodies.[48]

B-CELL ACTIVATING FACTOR

BAFF has received considerable attention in the field of SS research after it was reported that mice transgenic for BAFF develop a secondary pathology reminiscent of SS after exhibiting initial SLE-like disease manifestations.[82] Investigation of the BAFF system has demonstrated the need for an obligate survival signal for maturing and fully differentiated B cells.[83] Taken together, BAFF seems to lower the threshold required for B-cell receptor–mediated survival, potentially allowing autoreactive B cells to escape apoptosis and exhibit autoimmune potential.

In patients who have SS, elevated levels of circulating BAFF correlate with increased autoantibody titers.[84] Furthermore, increased BAFF expression is observed within salivary glands of patients who have SS,[85] together with a significantly lower rate of apoptosis among BAFF-expressing cells.[44] BAFF levels also are increased after discontinuation of anti-CD20 therapy; this may promote the reemergence of autoreactive B cells.[86] Counteracting BAFF-triggered repopulation of the periphery with pathogenic autoreactive B cells, therefore, may further improve the success of B-cell depletion in SS.[87]

B CELLS AND AUTOANTIBODIES

Patients who have pSS often have increased levels of polyclonal IgG (hypergammaglobulinemia) in the serum, together with autoantibodies specific for Ro/SSA and La/SSB.[79] Sixty percent to 80% of the patients present circulating anti-Ro and 40% to 60% anti-La antibodies, which are of equal importance in the diagnosis of SS. Even though the role of Ro/SSA and La/SSB in the pathogenesis of SS remains elusive, recent research efforts reanimated the discussion concerning the role of Ro52 as a direct contributor to the induction of autoimmune T cells and B cells in SS.[88] Immunization of Balb/c mice with specific Ro peptides has been shown to recapitulate the serologic pattern, pathologic findings, and salivary gland dysfunction of SS.[89]

Rheumatoid factor also is produced in approximately 60% of patients,[90] whereas anticyclic citrullinated peptide antibodies rarely are found.[91] Despite the predominance of T cells in the glandular lesions, strong lines of evidence suggest that B cells and autoantibodies may be more than just bystanders in disease pathogenesis.[92] Experiments in mice indicate that the occurrence of glandular inflammation is not dependent on antigen presentation by B cells, whereas hyposalivation seems to be crucially dependent on B cells and autoantibodies.[93] The exact mechanisms of how B-cell effector responses are involved in the pathogenesis of SS in humans is a subject of current research efforts.[92] Nonetheless, depletion of patient's B cells, using anti-CD20 antibodies, already has been shown to ameliorate several symptoms of the disease.[87]

SUMMARY

Although several hypotheses have been proposed over the years, the precise etiology and pathogenesis of SS remain elusive. A possible scenario for the emergence of SS

may comprise a viral infection of target organs interfering with innate immune mechanisms, leading to an inappropriate activation of the adaptive immune system, subsequently targeting self-determinants. Another concept presupposes that the genesis of autoimmune disease arises from defective immune regulation against key self-molecules. In such a case, self-antigens or other biologic agents, independent of their antigenic relationship with the actual disease-causing antigen, could be of benefit in the re-establishment of immunologic tolerance without resorting to long-term immunosuppression. Further investigations regarding regulatory processes in the progression of SS are necessary. Results published regarding anti-CD20 treatment in SS are encouraging and shed new light on the role of B cells in the pathogenesis and hopefully will soon provide physicians with an attractive option for treatment of SS. Advanced analytic platforms, such as multiplex immunoassays, mass spectrometry, and mRNA microarrays, play an important role in today's biomedical research and have to some extent been applied in SS-related context. The challenges in the years to come also will consist of drawing the right conclusions from such datasets and being able to adequately confirm the resulting hypotheses in experimental research. Successful validation of specific biomarkers and identification of therapeutic targets are the ultimate goal of such approaches, together with a more conceptual and integrated understanding of SS.

ACKNOWLEDGMENTS

The authors express their gratitude to current and former PhD and other research fellows who have profoundly contributed to lively discussions and a creative research environment. They also thank their administrative and laboratory staff for skillful and professional help. The patients donating cells, tissues, and biofluids are gratefully acknowledged together with the clinical staff at the Departments of Rheumatology and Otolaryngology/Head and Neck surgery, Haukeland University Hospital, Bergen, Norway.

REFERENCES

1. Jonsson R, Bowman SJ, Gordon TP. Sjögren's syndrome. In: Koopman WJ, editor. Arthritis and allied conditions. 15th edition. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 1681–705.
2. Delaleu N, Jonsson R, Koller MM. Sjögren's syndrome. Eur J Oral Sci 2005;113(2): 101–13.
3. Dawson LJ, Fox PC, Smith PM. Sjögren's syndrome—the non-apoptotic model of glandular hypofunction. Rheumatology (Oxford) 2006;45(7):792–8.
4. Champey J, Corruble E, Gottenberg JE, et al. Quality of life and psychological status in patients with primary Sjögren's syndrome and sicca symptoms without autoimmune features. Arthritis Rheum 2006;55(3):451–7.
5. Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjögren's syndrome: a prospective cohort study. Arthritis Rheum 2004; 50(4):1262–9.
6. Theander E, Henriksson G, Ljungberg O, et al. Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 2006;65(6):796–803.
7. Pflugfelder SC, Crouse CA, Monroy D, et al. Epstein-Barr virus and the lacrimal gland pathology of Sjögren's syndrome. Am J Pathol 1993;143(1):49–64.
8. Green JE, Hinrichs SH, Vogel J, et al. Exocrinopathy resembling Sjögren's syndrome in HTLV-1 tax transgenic mice. Nature 1989;341(6237):72–4.

9. Haddad J, Deny P, Munz-Gotheil C, et al. Lymphocytic sialadenitis of Sjögren's syndrome associated with chronic hepatitis C virus liver disease. Lancet 1992; 339(8789):321–3.
10. Cohen IR. The cognitive paradigm and the immunological homunculus. Immunol Today 1992;13(12):490–4.
11. Bolstad AI, Jonsson R. Genetic aspects of Sjögren's syndrome. Arthritis Res 2002;4(6):353–9.
12. Harangi M, Kaminski WE, Fleck M, et al. Homozygosity for the 168His variant of the minor histocompatibility antigen HA-1 is associated with reduced risk of primary Sjögren's syndrome. Eur J Immunol 2005;35(1):305–17.
13. Bolstad AI, Wargelius A, Nakken B, et al. Fas and Fas ligand gene polymorphisms in primary Sjögren's syndrome. J Rheumatol 2000;27(10):2397–405.
14. Magnusson V, Nakken B, Bolstad AI, et al. Cytokine polymorphisms in systemic lupus erythematosus and Sjögren's syndrome. Scand J Immunol 2001;54(1–2):55–61.
15. Gottenberg JE, Loiseau P, Azarian M, et al. CTLA-4 +49A/G and CT60 gene polymorphisms in primary Sjögren syndrome. Arthritis Res Ther 2007;9(2):R24.
16. Miceli-Richard C, Dieude P, Hachulla E, et al. Tumour necrosis factor receptor 2 (TNFRSF1B) association study in Sjögren's syndrome. Ann Rheum Dis 2007; 66(12):1684–5.
17. Kahlmann D, Davalos-Misslitz AC, Ohl L, et al. Genetic variants of chemokine receptor CCR7 in patients with systemic lupus erythematosus, Sjögren's syndrome and systemic sclerosis. BMC Genet 2007;8:33.
18. Triantafyllopoulou A, Tapinos N, Moutsopoulos HM. Evidence for coxsackievirus infection in primary Sjögren's syndrome. Arthritis Rheum 2004;50(9):2897–902.
19. Gottenberg JE, Pallier C, Ittah M, et al. Failure to confirm coxsackievirus infection in primary Sjögren's syndrome. Arthritis Rheum 2006;54(6):2026–8.
20. Hjelmervik TO, Petersen K, Jonassen I, et al. Gene expression profiling of minor salivary glands clearly distinguishes primary Sjögren's syndrome patients from healthy control subjects. Arthritis Rheum 2005;52(5):1534–44.
21. Hjelmervik TO, Lindqvist AK, Petersen K, et al. The influence of the NOD Nss1/Idd5 loci on sialadenitis and gene expression in salivary glands of congenic mice. Arthritis Res Ther 2007;9(5):R99.
22. Killedar SJ, Eckenrode SE, McIndoe RA, et al. Early pathogenic events associated with Sjögren's syndrome (SjS)-like disease of the NOD mouse using microarray analysis. Lab Invest 2006;86(12):1243–60.
23. Båve U, Nordmark G, Lövgren T, et al. Activation of the type I interferon system in primary Sjögren's syndrome: a possible etiopathogenic mechanism. Arthritis Rheum 2005;52(4):1185–95.
24. Lovgren T, Eloranta ML, Kastner B, et al. Induction of interferon-alpha by immune complexes or liposomes containing systemic lupus erythematosus autoantigen- and Sjögren's syndrome autoantigen-associated RNA. Arthritis Rheum 2006; 54(6):1917–27.
25. Laine M, Porola P, Udby L, et al. Low salivary dehydroepiandrosterone and androgen-regulated cysteine-rich secretory protein 3 levels in Sjögren's syndrome. Arthritis Rheum 2007;56(8):2575–84.
26. Shim GJ, Warner M, Kim HJ, et al. Aromatase-deficient mice spontaneously develop a lymphoproliferative autoimmune disease resembling Sjögren's syndrome. Proc Natl Acad Sci U S A 2004;101(34):12628–33.
27. Kuroki M, Okayama A, Nakamura S, et al. Detection of maternal-fetal microchimerism in the inflammatory lesions of patients with Sjögren's syndrome. Ann Rheum Dis 2002;61(12):1041–6.

28. Masago R, Aiba-Masago S, Talal N, et al. Elevated proapoptotic Bax and caspase 3 activation in the NOD.scid model of Sjögren's syndrome. Arthritis Rheum 2001;44(3):693–702.
29. Li H, Dai M, Zhuang Y. A T cell intrinsic role of Id3 in a mouse model for primary Sjögren's syndrome. Immunity 2004;21(4):551–60.
30. Hayakawa I, Tedder TF, Zhuang Y. B-lymphocyte depletion ameliorates Sjögren's syndrome in Id3 knockout mice. Immunology 2007;122(1):73–9.
31. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature 1998;392(6673):245–52.
32. Steinman RM, Nussenzweig MC. Avoiding horror autotoxicus: the importance of dendritic cells in peripheral T cell tolerance. Proc Natl Acad Sci U S A 2002;99(1):351–8.
33. Banchereau J, Pascual V, Palucka AK. Autoimmunity through cytokine-induced dendritic cell activation. Immunity 2004;20(5):539–50.
34. Tarbell KV, Yamazaki S, Steinman RM. The interactions of dendritic cells with antigen-specific, regulatory T cells that suppress autoimmunity. Semin Immunol 2006;18(2):93–102.
35. Enk AH. Dendritic cells in tolerance induction. Immunol Lett 2005;99(1):8–11.
36. Ludewig B, Odermatt B, Landmann S, et al. Dendritic cells induce autoimmune diabetes and maintain disease via de novo formation of local lymphoid tissue. J Exp Med 1998;188(8):1493–501.
37. Dittel BN, Visintin I, Merchant RM, et al. Presentation of the self antigen myelin basic protein by dendritic cells leads to experimental autoimmune encephalomyelitis. J Immunol 1999;163(1):32–9.
38. Chen M, Wang YH, Wang Y, et al. Dendritic cell apoptosis in the maintenance of immune tolerance. Science 2006;311(5764):1160–4.
39. Chen M, Huang L, Wang J. Deficiency of Bim in dendritic cells contributes to overactivation of lymphocytes and autoimmunity. Blood 2007;109(10):4360–7.
40. Gottenberg JE, Cagnard N, Lucchesi C, et al. Activation of IFN pathways and plasmacytoid dendritic cell recruitment in target organs of primary Sjögren's syndrome. Proc Natl Acad Sci U S A 2006;103(8):2770–5.
41. Vogelsang P, Jonsson MV, Dalvin ST, et al. Role of dendritic cells in Sjögren's syndrome. Scand J Immunol 2006;64(3):219–26.
42. Delaleu N, Immervoll H, Cornelius J, et al. Biomarker profiles in serum and saliva of experimental Sjögren's syndrome: associations with specific autoimmune manifestations. Arthritis Res Ther 2008;10(1):R22.
43. Barone F, Bombardieri M, Manzo A, et al. Association of CXCL13 and CCL21 expression with the progressive organization of lymphoid-like structures in Sjögren's syndrome. Arthritis Rheum 2005;52(6):1773–84.
44. Szodoray P, Jellestad S, Teague MO, et al. Attenuated apoptosis of B cell activating factor-expressing cells in primary Sjögren's syndrome. Lab Invest 2003;83(3):357–65.
45. Charo IF, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 2006;354(6):610–21.
46. Amft N, Bowman SJ. Chemokines and cell trafficking in Sjögren's syndrome. Scand J Immunol 2001;54(1–2):62–9.
47. Salomonsson S, Jonsson MV, Skarstein K, et al. Cellular basis of ectopic germinal center formation and autoantibody production in the target organ of patients with Sjögren's syndrome. Arthritis Rheum 2003;48(11):3187–201.
48. Delaleu N, Madureira AC, Immervoll H, et al. Inhibition of experimental Sjögren's syndrome through immunization with HSP60 and its peptide amino acids 437–460. Arthritis Rheum 2008;58(8):2318–28.

49. Jonsson MV, Salomonsson S, Øijordsbakken G, et al. Elevated serum levels of soluble E-cadherin in patients with primary Sjögren's syndrome. Scand J Immunol 2005;62(6):552–9.
50. Manoussakis MN, Boiu S, Korkolopoulou P, et al. Rates of infiltration by macrophages and dendritic cells and expression of interleukin-18 and interleukin-12 in the chronic inflammatory lesions of Sjögren's syndrome: correlation with certain features of immune hyperactivity and factors associated with high risk of lymphoma development. Arthritis Rheum 2007;56(12):3977–88.
51. Spachidou MP, Bourazopoulou E, Maratheftis CI, et al. Expression of functional Toll-like receptors by salivary gland epithelial cells: increased mRNA expression in cells derived from patients with primary Sjögren's syndrome. Clin Exp Immunol 2007;147(3):497–503.
52. Kawakami A, Nakashima K, Tamai M, et al. Toll-like receptor in salivary glands from patients with Sjögren's syndrome: functional analysis by human salivary gland cell line. J Rheumatol 2007;34(5):1019–26.
53. Li X, Li X, Qian L, et al. T regulatory cells are markedly diminished in diseased salivary glands of patients with primary Sjögren's syndrome. J Rheumatol 2007; 34(12):2438–45.
54. Sharma R, Zheng L, Guo X, et al. Novel animal models for Sjögren's syndrome: expression and transfer of salivary gland dysfunction from regulatory T cell-deficient mice. J Autoimmun 2006;27(4):289–96.
55. Gottenberg JE, Lavie F, Abbed K, et al. CD4 CD25high regulatory T cells are not impaired in patients with primary Sjögren's syndrome. J Autoimmun 2005;24(3): 235–42.
56. Salam MA, Matin K, Matsumoto N, et al. E2f1 mutation induces early onset of diabetes and Sjögren's syndrome in nonobese diabetic mice. J Immunol 2004; 173(8):4908–18.
57. Chatenoud L. Immune therapies of autoimmune diseases: are we approaching a real cure? Curr Opin Immunol 2006;18(6):710–7.
58. Chatenoud L, Bluestone JA. CD3-specific antibodies: a portal to the treatment of autoimmunity. Nat Rev Immunol 2007;7(8):622–32.
59. Curtis JR, Xi J, Patkar N, et al. Drug-specific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(12):4226–7.
60. Jonsson MV, Skarstein K, Jonsson R, et al. Serological implications of germinal center-like structures in primary Sjögren's syndrome. J Rheumatol 2007;34(10):2044–9.
61. Szodoray P, Alex P, Jonsson MV, et al. Distinct profiles of Sjögren's syndrome patients with ectopic salivary gland germinal centers revealed by serum cytokines and BAFF. Clin Immunol 2005;117(2):168–76.
62. Jonsson MV, Szodoray P, Jellestad S, et al. Association between circulating levels of the novel TNF family members APRIL and BAFF and lymphoid organization in primary Sjögren's syndrome. J Clin Immunol 2005;25(3):189–201.
63. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum 2002;46(3):741–7.
64. Takemura S, Braun A, Crowson C, et al. Lymphoid neogenesis in rheumatoid synovitis. J Immunol 2001;167(2):1072–80.
65. Armengol MP, Juan M, Lucas-Martin A, et al. Thyroid autoimmune disease: demonstration of thyroid antigen-specific B cells and recombination-activating gene expression in chemokine-containing active intrathyroidal germinal centers. Am J Pathol 2001;159(3):861–73.

66. Mazzucchelli L, Blaser A, Kappeler A, et al. BCA-1 is highly expressed in *Helicobacter pylori*-induced mucosa-associated lymphoid tissue and gastric lymphoma. J Clin Invest 1999;104(10):R49–54.
67. Feldmann M. Development of anti-TNF therapy for rheumatoid arthritis. Nat Rev Immunol 2002;2(5):364–71.
68. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled trial of remicade in primary Sjögren's syndrome (TRIPSS). Arthritis Rheum 2004;50(4):1270–6.
69. Konttinen YT, Kemppinen P, Koski H, et al. T(H)1 cytokines are produced in labial salivary glands in Sjögren's syndrome, but also in healthy individuals. Scand J Rheumatol 1999;28(2):106–12.
70. Fox RI, Kang HI, Ando D, et al. Cytokine mRNA expression in salivary gland biopsies of Sjögren's syndrome. J Immunol 1994;152(11):5532–9.
71. van Blokland SC, Versnel MA. Pathogenesis of Sjögren's syndrome: characteristics of different mouse models for autoimmune exocrinopathy. Clin Immunol 2002; 103(2):111–24.
72. Mitsias DI, Tzioufas AG, Veiopoulou C, et al. The Th1/Th2 cytokine balance changes with the progress of the immunopathological lesion of Sjögren's syndrome. Clin Exp Immunol 2002;128(3):562–8.
73. Jonsson MV, Delaleu N, Brokstad KA, et al. Impaired salivary gland function in NOD mice: association with changes in cytokine profile but not with histopathologic changes in the salivary gland. Arthritis Rheum 2006;54(7):2300–5.
74. Gao J, Killedar S, Cornelius JG, et al. Sjögren's syndrome in the NOD mouse model is an interleukin-4 time-dependent, antibody isotype-specific autoimmune disease. J Autoimmun 2006;26(2):90–103.
75. Brayer JB, Cha S, Nagashima H, et al. IL-4-dependent effector phase in autoimmune exocrinopathy as defined by the NOD.IL-4-gene knockout mouse model of Sjögren's syndrome. Scand J Immunol 2001;54(1-2):133–40.
76. Nguyen CQ, Gao JH, Kim H, et al. IL-4-STAT6 signal transduction-dependent induction of the clinical phase of Sjögren's syndrome-like disease of the nonobese diabetic mouse. J Immunol 2007;179(1):382–90.
77. Weaver CT, Hatton RD, Mangan PR, et al. IL-17 family cytokines and the expanding diversity of effector T cell lineages. Annu Rev Immunol 2007;25:821–52.
78. Nguyen CQ, Hu MH, Li Y, et al. Salivary gland tissue expression of interleukin–23 and interleukin–17 in Sjögren's syndrome: findings in humans and mice. Arthritis Rheum 2008;58(3):734–43.
79. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European consensus group. Ann Rheum Dis 2002;61(6):554–8.
80. Hu S, Wang J, Meijer J, et al. Salivary proteomic and genomic biomarkers for primary Sjögren's syndrome. Arthritis Rheum 2007;56(11):3588–600.
81. Veenstra TD. Global and targeted quantitative proteomics for biomarker discovery. J Chromatogr B Analyt Technol Biomed Life Sci 2007;847(1):3–11.
82. Groom J, Kalled SL, Cutler AH, et al. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjögren's syndrome. J Clin Invest 2002; 109(1):59–68.
83. Mackay F, Schneider P, Rennert P, et al. BAFF AND APRIL: a tutorial on B cell survival. Annu Rev Immunol 2003;21:231–64.
84. Mariette X, Roux S, Zhang J, et al. The level of BLyS (BAFF) correlates with the titre of autoantibodies in human Sjögren's syndrome. Ann Rheum Dis 2003; 62(2):168–71.

85. Daridon C, Devauchelle V, Hutin P, et al. Aberrant expression of BAFF by B lymphocytes infiltrating the salivary glands of patients with primary Sjögren's syndrome. Arthritis Rheum 2007;56(4):1134–44.
86. Lavie F, Miceli-Richard C, Ittah M, et al. Increase of B cell-activating factor of the TNF family (BAFF) after rituximab treatment: insights into a new regulating system of BAFF production. Ann Rheum Dis 2007;66(5):700–3.
87. Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum 2007; 57(2):310–7.
88. Espinosa A, Zhou W, Ek M, et al. The Sjögren's syndrome-associated autoantigen Ro52 is an E3 ligase that regulates proliferation and cell death. J Immunol 2006; 176(10):6277–85.
89. Scofield RH, Asfa S, Obeso D, et al. Immunization with short peptides from the 60-kDa Ro antigen recapitulates the serological and pathological findings as well as the salivary gland dysfunction of Sjögren's syndrome. J Immunol 2005; 175(12):8409–14.
90. Muller K, Manthorpe R, Permin H, et al. Circulating IgM rheumatoid factors in patients with primary Sjögren's syndrome. Scand J Rheumatol Suppl 1988;75: 265–8.
91. Gottenberg JE, Mignot S, Nicaise-Rolland P, et al. Prevalence of anti-cyclic citrullinated peptide and anti-keratin antibodies in patients with primary Sjögren's syndrome. Ann Rheum Dis 2005;64(1):114–7.
92. Dawson LJ, Stanbury J, Venn N, et al. Antimuscarinic antibodies in primary Sjögren's syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells. Arthritis Rheum 2006;54(4):1165–73.
93. Robinson CP, Brayer J, Yamachika S, et al. Transfer of human serum IgG to nonobese diabetic Igmu null mice reveals a role for autoantibodies in the loss of secretory function of exocrine tissues in Sjögren's syndrome. Proc Natl Acad Sci U S A 1998;95(13):7538–43.

Genes and Sjögren's Syndrome

Beth L. Cobb, MBA[a], Christopher J. Lessard, BS[a,b], John B. Harley, MD, PhD[a,c,d], Kathy L. Moser, PhD[a,*]

KEYWORDS

• Sjögren's syndrome • Genetics • HLA • Association

Sjögren's syndrome (SS) is a chronic, progressive exocrinopathy characterized by infiltration and proliferation of lymphocytes into affected glands. Although patients are clinically identified through oral and ocular features, the full spectrum of disease encompasses a complex and myriad systemic symptoms. The primary pathophysiology includes concurrent mechanisms of dysregulated innate immunity and adaptive autoimmunity involving cell-mediated and humoral disease processes. Etiology involves environmental and genetic factors; however, large-scale genetic studies have not yet been conducted in SS and the genetic basis for SS is largely unexplored.

Although few genetic studies have been completed to date in SS, the overall evidence to support a genetic basis for SS continues to grow. Current data strongly suggest SS is a complex, polygenic disorder likely sharing common genetic determinants with related autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Recent advances in SLE and RA provide valuable insight into the potential genetic complexity of SS. This article reviews association studies in various candidate genes for SS completed to date and highlights insights from SS mouse models. Advanced genetic and genomic technologies now are available for assaying gene expression and genetic associations across the entire genome, providing important opportunities to conduct unbiased interrogation of essentially every gene for a role in SS.

Supported by NIH grants DE015223, AR42460, AR12253, AR48940, AR62277, RR020143, AI24717, a Department of Veteran Affairs Merit Award (JBH), AR050782, and AR043274 (KLM) and the Alliance for Lupus Research.

[a] Arthritis and Immunology Program, Oklahoma Medical Research Foundation, 825 NE 13th Street, Oklahoma City, OK 73104, USA

[b] Department of Pathology, University of Oklahoma Health Sciences Center, 940 Stanton L. Young Boulevard, BMS 451, Oklahoma City, OK 73104, USA

[c] Department of Medicine, University of Oklahoma Health Sciences Center, 920 Stanton L. Young Boulevard, WP1140, Oklahoma City, OK 73104 USA

[d] US Department of Veterans Affairs Medical Center, 921 NE 13 Street, Oklahoma City, OK 73104, USA

* Corresponding author.

E-mail address: moserk@omrf.org (K.L. Moser).

Rheum Dis Clin N Am 34 (2008) 847–868

doi:10.1016/j.rdc.2008.08.003 **rheumatic.theclinics.com**

0889-857X/08/$ – see front matter

GENETIC EPIDEMIOLOGY

SS is a common condition that disproportionately affects women by an odds ratio of more than 9:1 and usually presents during the fourth or fifth decade of life. Patients typically are classified as having primary SS (pSS) when additional autoimmune diseases are not evident or secondary SS (sSS) when a concurrent diagnosis of a well-defined autoimmune disease is recognized. Estimates of the prevalence of primary SS worldwide range from 0.2% to 3.39% (ie, 200–3390 cases/100,000 population); however, most estimates are closer to 0.5% to 0.7%.[1–6] Ethnic specific prevalence rates outside of European and North American cohorts have not been well defined. At present, there is no evidence to suggest temporal or geographic clustering of SS.

Similar to related autoimmune diseases, such as SLE and RA, susceptibility to SS likely is complex and results from variation in multiple genes.[1] Evidence for a genetic component often is derived from studies demonstrating increased concordance rates among monozygotic twins and familial aggregation. Several case reports of twins who had SS have been published, but reliable twin concordance rates have not been estimated.[7–10] Scofield and colleagues[10] reported a case of monozygotic twins who had SS and who had anti-60 kD Ro/SSA autoantibodies in their sera. In 2005, Houghton and colleagues[9] described a case of adolescent dizygotic twins who shared a diagnosis of pSS. One of the two sisters presented with pulmonary symptoms, uncommon in pediatric pSS. Given the many inter-relationships between SS and SLE and RA, twin concordance could be expected to be between those of RA (15%) and SLE (25%), with a female sibling or fraternal twin rate of 2% to 4% and estimated odds of female sibling concordance (λ_s) between 8 and 20.

Several families multiplex for SS have been described,[11–16] and family history with relatives having other autoimmune disease is common (30%–35%), often including SS (12%), autoimmune thyroid disease (AITD) (14%), RA (14%), and SLE (5%–10%).[14,17] In a pedigree of 60 members, eight were found to share a diagnosis of SLE. Among eight individuals who had SLE, all shared positive antinuclear autoantibodies, six shared pleuritis and malar rash, five reported photosensitivity, and four shared nephritis. Of the 51 relatives who contributed samples and for whom results were obtained, 29% had autoantibodies and 18% had autoimmune disease, including one who had SS.[16]

RELATED AUTOIMMUNE DISEASES

In humans, clustering of autoimmune diseases such as SLE, RA, AITD, psoriasis, multiple sclerosis, and SS within families frequently has been documented.[18] Autoimmune serologic abnormalities are frequent (up to 55%, depending on the antibody specificity) in otherwise healthy family members.[19] Sharing of clinical and serologic features among related diseases also occurs. For example, subsets of patients who have SLE or SS may share similar symptoms (commonly including arthralgias, myalgias, fatigue, rashes, and visceral involvement from vasculitis) or serologic abnormalities, such as antinuclear autoantibodies, anti-Ro/SSA, or anti-La/SSB autoantibodies.[20] Some features of SS are shared more commonly with RA patients, such as arthritis and production of rheumatoid factor antibodies. Furthermore, in studies using high-density gene expression microarrays, the authors and colleagues have identified key disease pathways that are present in multiple disease phenotypes. For example, pathways known to be inducible by interferons (IFNs) are commonly dysregulated in certain subsets of patients across multiple autoimmune diseases, including SLE and SS.[21]

Several genetic loci are shown to be involved in the etiology of multiple autoimmune diseases in humans and support sharing of underlying disease mechanisms across related phenotypes. Associations of certain HLA loci with autoimmune diseases has been reported extensively in SS, SLE, RA, ankylosing spondylitis, psoriasis, multiple sclerosis, and type 1 diabetes.[22] A growing list of non-HLA genes also has been implicated in multiple autoimmune diseases. Examples include associations of cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) with AITD, type 1 diabetes mellitus (T1D), celiac disease, Wegener's granulomatosis, SLE, vitiligo, Addison's disease, and RA;[23–30] Programmed Death 1(PD-1) with RA, T1D, and SLE;[31] and protein tyrosine phosphatase nonreceptor type 22 (PTPN22) with SLE, RA, T1D, Graves' disease, and Hashimoto's thyroiditis.[32–37] Interferon regulatory factor 5 (IRF5) and signal transducer and activator of transcription 4 (STAT4) are genes strongly associated with SLE for which there are recent data suggesting association in pSS.[38] Murine studies also are consistent with models of multigenic inheritance, and many susceptibility loci have been identified that are shared across different autoimmune mouse models for SS and other autoimmune diseases.[39]

GENETIC DISCOVERY IN SJÖGREN'S SYNDROME

The advent of affordable, high-throughput genotyping technology has led to a surge in genetic discovery for complex diseases. Microarray-based platforms can now interrogate over 1 million markers of genetic variation in a single experiment and provide technical capacity for genome-wide association studies. This approach has been exceptionally fruitful for prostate cancer, breast cancer, and autoimmune diseases, such as T1D, RA, and SLE.[40–45] For example, more than 25 genes/loci in which genetic association with SLE is established are now recognized. Ongoing studies are expected to continue to reveal additional genes that contribute to SLE.

SS has been vastly understudied compared with related autoimmune diseases. A major contributing factor revolves around difficulties with patient classification and availability of multiple, large, independent cohorts of well-characterized patients for genetic studies. Ideally, assembly of cohorts for genetic studies involves multidisciplinary teams of investigators to ensure accurate, uniform phenotyping of oral, ocular, and systemic features of pSS. Classification issues have been addressed most recently by an international group on Sjögren's syndrome diagnostic criteria. Their efforts led to publication of an American-European Consensus Group report describing a revision of the 1993 European criteria.[46,47] A critical consequence of this classification scheme is that to be classified as having pSS, patients must have positive salivary gland histopathology or autoantibodies (anti-Ro/SSA or anti-La/SSB) with additional criteria in varying combinations. Labial salivary gland biopsies are not routine in clinical practice, which may lead to exclusion of a considerable number of patients who have classical clinical features of SS but who are seronegative for anti-Ro/SSA or anti-La/SSB.[48] Furthermore, misdiagnosis (particularly with SLE, RA, or multiple sclerosis) and underdiagnosis (many physicians fail to recognize or are not acutely familiar with SS) frequently occurs in routine clinical practice, making large-scale nationwide recruitment efforts problematic. In part because of these issues, there have been no reports of organized pSS genome scans.

Table 1 delineates the number of patient samples that are required to detect genetic associations of small effects and achieve 80% power using an additive genetic model. If the prevalence of SS is assumed to be 0.2% and the risk allele frequency (minor allele frequency) is 0.2%, then 4772 cases and 4772 controls are required to detect associations with an allelic odds ratio of 1.2 in a genome scan. However, 1785 cases

Table 1
Sample size requirements to detect genetic effects using 1, 100, or 1 million markers with 80% power

No. of Independent Tests	Percent Prevalence	Minor Allele Frequency (%)	Allelic Odds Ratio	No. of Cases	No. of Controls	*P* Value
1	0.2	0.2	1.2	940	940	0.05
1	0.5	0.2	1.2	352	352	0.05
1	0.2	0.2	1.5	195	195	0.05
1	0.5	0.2	1.5	100	100	0.05
100	0.2	0.2	1.2	2246	2246	0.0005
100	0.5	0.2	1.2	840	840	0.0005
100	0.2	0.2	1.5	465	465	0.0005
100	0.5	0.2	1.5	163	163	0.0005
1,000,000	0.2	0.2	1.2	4772	4772	0.00000005
1,000,000	0.5	0.2	1.2	1785	1785	0.00000005
1,000,000	0.2	0.2	1.5	980	980	0.00000005
1,000,000	0.5	0.2	1.5	345	345	0.00000005

The values in this table were obtained using the CaTS Power Calculator.
Data from Skol AD, Scott LJ, Abecasis GR, et al. Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. Nat Genet 2006;38(2):209–13.

and 1785 controls are required to detect associations for the same genome scan if the prevalence is assumed to be 0.5%. Candidate gene association studies in SS have only been conducted for approximately 20 loci to date, which is less that 0.1% of the estimated 20,000 genes in the human genome. Furthermore, studies published to date typically evaluated samples sizes of 200 cases/200 controls or fewer for association to a single or limited number of polymorphisms. Although candidate gene studies typically require smaller sample sizes because of the reduced number of independent statistical tests performed, independent replication of any genetic association is critical and remains to be accomplished for several of the genetic effects reported in pSS to date.

HLA Associations

Historically, HLA studies in SS dominated the literature before 1995. In humans, the 3.6-megabase (Mb) major histocompatability complex (MHC) region on chromosome 6 contains 140 genes between flanking genetic markers MOG and COL11A2.[49] The most well-characterized genes in the MHC region are the subset that encodes cell-surface antigen-presenting proteins. These genes, referred to as HLA genes, are well-documented risk factors for the development of autoimmune disorders.[50,51] As with most autoimmune diseases, associations of HLA loci (mostly class II genes) have been described and vary in different ethnic groups with SS.[1] In most studies, when an HLA association with pSS was demonstrable, a stronger association could be found to the anti-Ro/SSA and anti-La/SB autoantibody responses.

As shown in **Table 2**, HLA-DR and -DQ alleles represent the most common associations studied in SS.[14] The first HLA class II associations described were at the DR3[52–54] and DR2[17,54] loci in white populations. Together these two HLA sub-types were shown to account for up to 90% of the MHC association in patients who had SS.[17] These associations have been confirmed in the majority of subsequent studies evaluating northern European cohorts (see **Table 2**). In 2005, Anaya and

Table 2
HLA associations with primary Sjögren's syndrome

Population	Polymorphism	Cases/ Controls	Phenotype	Study
European	DRB1*1501/*0301	42/200	pSS	Guggenbuhl et al[56]
	DRB1*15	19/118	sSS	Mattey et al[57]
	DRB1*0301	29/181	pSS & anti-Ro52	Nakken et al[58]
	DRB1*0101	29/181	pSS & anti-Ro52	Nakken et al[58]
	DRB1*0501	29/181	anti-Ro52	Nakken et al[58]
	DRB1*03-DQB1* 02-DQA1*0501	62/64	anti-Ro with anti-La	Bolstad et al[59]
	DQB1*0201	29/181	anti-Ro52	Nakken et al[58]
	DRB1*0301- DRB3*0101-	73/135	pSS	Kang et al[60]
	DQA1*0501-			
	DQB*0201			
	DR3-DQA1*0501-	80/164	pSS with anti-La	Rischmueller et al[61]
	DQB1*02			
	DR2-DQA1*0102-	80/164	pSS with anti-Ro, no anti-La	Rischmueller et al[61]
	DQB1*0602			
Japanese	DRB1*8032/ DQA1*0103/ DQB1*0601	41/525	anti-Ro with anti-La	Miyagawa et al[62]
	DRB1*8032	41/525	anti-Ro with anti-La	Miyagawa et al[62]
	DRB1*0405- DRB4*0101-	33/49	pSS	Kang et al[60]
	DQA1*0301-			
	DQB1*0401			
Chinese	DRB1*0803/	42/43	pSS	Kang et al[60]
	DQA1*0103-			
	DQB1*0601			
European and African American	DQB1*0201-	67/00	anti-Ro	Scofield et al[63]
	DQA1*0101			
	(or –DQA1*0102 or DQA1*0103)			
Tunisian	DQB1 CAR1/CAR2	58/147	pSS	Hadj Kacem et al[64]

colleagues[55] demonstrated that the HLA-DRB1*0301-DQB1*0201 haplotype was associated with pSS disease in Latin Americans. The possibility that both of these alleles play a role was reinforced in a 1998 study, which found the strongest disease susceptibility association with heterozygosity for DRB1*1501(DR2) and DRB1*0301(DR3).[53]

The HLA-DR3 haplotype, associated with SS and SLE, is within a region with extended linkage disequilibrium not observed other places in the genome. In general, linkage disequilibrium can be extinguished more than 30 to 60 kilobases (kb) in

either direction. Graham and colleagues[22] found that the SLE risk region on DRB1*0301-containing haplotypes was no less than approximately 1 Mb. The risk haplotype containing DRB1*1501 (DR2), however, was much smaller and contained within approximately 500 kb. It is clear that haplotypes cooperate. In 1986, Harley and colleagues[65] reported that heterozygosity for DQw1 and DQw2 alleles are associated with high concentrations of anti-Ro/SSA and anti-La/SSB in pSS.

The HLA class I genetic associations with pSS are less powerful than the HLA associations at HLA-DR and HLA-DQ. Association with the HLA class 1 allele, B8, was first reported in 1975.[66,67] In 2001, Loiseau and colleagues[68] reported association with the HLA class 1 allele, A24. The results from this study showed that HLA-A24 is associated more often with DRB1*11-DQB1*0301 or DRB1*0301-DQB1*02 in pSS.

The evidence for association of some genes in the MHC, such as tumor necrosis factor (TNF)-α and the transporter 2, ATP-binding cassette, subfamily B (TAP2), may be stronger in patients who are seropositive for anti-Ro/SSA. Guggenbuhl and colleagues[69] analyzed TNF-α microsatellites in a group of 35 patients who had pSS and 146 healthy controls and found an association between joint symptoms or anti-Ro/SSA autoantibodies in patients who had pSS and TNF-α10. In contrast, Jean and colleagues[70] found no association between these two subgroups of patients who had pSS and TNF-α alleles. Polymorphisms of TAP2 gene, were studied in a collection of 108 Japanese patients who had SS and 160 controls. A formerly unknown TAP2 allele, Bky2, was found in increased frequency in patients versus controls ($P < .05$).[71] In addition, the level of anti-Ro/SSA autoantibody was significantly increased in patients carrying the Bky2 risk allele ($P = .001$).[71] This association was not confirmed in a cohort of 45 patients and 200 controls reported by Jean and colleagues.[70]

Non-HLA Associations

Evidence for association between SS and several non-HLA genes has been reported. These association studies have been performed in various populations, largely from outside the United States, and have involved small cohorts of patients who had SS (<200 cases). All reported non-HLA region associations and subsequent repudiations can be found in **Table 3**, some of which have been associated with pSS or various forms of sSS or specific autoantibodies.

Cytokine Polymorphisms

Cytokine gene polymorphisms in interleukin (IL)-10, IL-6, IL-1 receptor antagonist (IL-1RA), IL-4 receptor alpha (IL-4Rα), TNF-α, IFN-γ, and transforming growth factor-beta 1 (TGF-β1) have been associated with pSS (see **Table 3**). IL-10 is a cytokine produced primarily by monocytes that enhances B-cell proliferation and antibody production. In a study of 62 patients who had pSS and 400 healthy controls, Hulkkonen and colleagues[82,99] found that the IL-10 GCC haplotype was associated with pSS ($P = .011$). Using a collection of 108 patients who had pSS and 165 matched controls, however, Limaye and colleagues[83] were unable to confirm association with anti-Ro/SSA or pSS with IL-10 polymorphisms.

IL-6 also is involved in B-cell proliferation and antibody production. In a study of 66 patients who had pSS and 400 healthy controls, Hulkkonen and colleagues[82] found that IL-6 levels increased in parallel with the number of pSS criteria fulfilled. No genetic association, however, was found between IL-6 and pSS in a study of 129 French patients who had pSS and 96 healthy controls.[98]

The IL1RN*2 allele polymorphism of IL-1RA is believed to play a role in many autoimmune disorders. Perrier and colleagues[78] reported an increased frequency of the

IL1RN*2 polymorphism in 36 patients who had SS relative to patients who had possible pSS. In addition, IL-1RA serum levels were elevated in patients who had SS compared with controls. Petrek and colleagues[73] genotyped IL-1RA in a collection of 39 patients who had SS and 76 healthy controls and observed no difference in the allele frequency of IL-1RA polymorphisms between cases and controls.

IL-4Rα gene has been evaluated in several studies for association in pSS. Youn and colleagues[79] observed an increased frequency of the Q551 allele in 45 Korean patients who had SS compared with 74 healthy controls. Another study demonstrated that patients who had pSS and carried the ARSPRV haplotype had an increase in the frequency of rheumatoid factor and other immunologic markers. In addition, a higher frequency of parotid gland enlargement in patients who had pSS was found in this study.[81] Meanwhile, the R576 polymorphism of IL-4Rα was not found associated with pSS by Lester and colleagues.[80]

Transforming Growth Factor-Beta 1

TGF-β1 has been implicated in the pathogenesis of pSS.[69] TGF-β1 is a profibrotic, immunosuppressive cytokine expressed by many cell types and is known to be underexpressed in salivary glands of patients who have SS compared with controls.[98] Gottenberg and colleagues[98] analyzed several cytokine gene polymorphisms, including TGF-β1, in a study of 129 French patients who had pSS and 96 controls. At codon 10 of TGF-β1, the frequency of allele C was elevated in patients who had pSS and anti-La/SSB autoantibodies and patients who carried the HLA-DRB1*3 haplotype. They hypothesized that the TGF-β1 polymorphism and the HLA-DRB1*3 haplotype act in combination to promote the production of anti-La/SSB autoantibodies.

Signal Transducer and Activator of Transcription 4

The most recently published association in pSS is with a single nucleotide polymorphism (SNP), rs7574865, found in the STAT4 gene.[38] STAT4 is a lymphocyte signal transduction molecule involved in IL-12 and IL-13 signaling.[38] STAT4, a member of the STAT family of transcription factors, encodes a protein that transmits signals induced by IL-12, type 1 IFNs, IL-23.33, and other cytokines. Upon activation by cytokines, STAT4 stimulates transcription of IFN-γ, a key inducer of T-cell differentiation into type 1 helper T cells. The protein encoded by STAT4 is required to regulate helper T-cell responses.[100,101] SNPs in the STAT4 gene also have been found strongly associated with SLE and RA.[102]

Interferon Regulatory Factor 5

IRF5, a member of a family of transcription factors, acts downstream of Toll-like receptors (TLRs) and type 1 IFN stimulation to promote the expression of proinflammatory cytokines, including IFN-α.[103,104] In a collection of 210 pSS cases and 154 healthy controls, a GT or TT genotype at the IRF5 SNP, rs2004640, was found in 87% of patients compared with 77% of controls (OR 1.93). The T allele results in the expression of the exon 1B isoform and significant over-expression of IRF5 in SLE cell lines.[105] This gene has been associated with SLE in genetic studies of Asian, white, Hispanic, and African American populations with several independent genetic effects within the IRF5 locus conferring risk.[106–112]

Protein Tyrosine Phosphatase Nonreceptor Type 22

PTPN22 is expressed primarily in lymphoid tissues. This gene encodes for the protein, Lyp, that dephosphorylates kinases, Lck, Fyn, and Zap-70, all known to have prominent roles in T-cell signaling. Moreover, this protein has a C-terminus binding site for

Table 3
Summary of non-HLA association studies in primary Sjögren's syndrome

				Positive Association		Negative Association	
Gene	Site of Polymorphism	Allele or Genotype	Phenotype	Reference	Cases/ Controls	Reference	Cases/ Controls
ApoE		ApoE ε4	Early-onset pSS	Pertovaara et al[72]	63/64		
CCR5		CCR5Δ32	pSS	Petrek et al[73]	39/76		
Fas	Nucleotide -671	G/G	pSS	Bolstad et al[74]	70/72	Mullighan et al[75]	108/101
	IVS2nt176	SNP C/T					
	IVS5nt82	SNP C/G					
GSTM1		Homozygous null genotype	pSS	Morinobu et al[76]	106/143		
HA-1	Nucleotide + 500/504	168His	pSS	Harangi et al[77]	88/371		
IL-1RA	Intron 2	IL1RN*2	pSS	Perrier et al[78]	36/100	Petrek et al[73]	39/76
IL-4Rα		Q576R	pSS	Youn et al[79]	45/74	Lester et al[80]	98/164
						Ramos-Casals et al[81]	48/98
IL-10	Promoter-1082	SNP G/A	pSS	Hulkkonen et al[82]	66/400	Limaye et al[83]	108/165
	Promoter-819	SNP C/T					
	Promoter-592	SNP C/A					
	Promoter-1082, -819, -592	ATA/ATA		Origuchi et al[84]	47/107		
	Promoter-1082, -819, -592	GCC/ATA	Early-onset pSS	Font et al[85]	63/150		
Immunoglobulin KM		KM1	Anti-La in pSS	Whittingham et al[86]	26/1204	Downie-Doyle et al[87]	109/164

IRF5	Two from exon 1B	Rs2004640T	pSS	Miceli-Richard et al[88]	210/154		
MBL	Codon 54	Wild-type allele	pSS	Wang et al[89]	104/143	Mullighan et al[90]	97/106
						Aittoniemi et al[91]	62/400
		Homozygous mutant allele	Lupus, RA, SS	Tsutsumi et al[92]	266/129		
PTPN22	Nucleotide 1858	SNP C/T	pSS	Gomez et al[93]	70/308	Ittah et al[94]	183/172
						Criswell et al[18]	16/2064
Ro52	Intron 1 (nucleotide 7216)	SNP C/T	Anti-Ro in SS	Nakken et al[95]	97/70		
	Intron 3 (137 from exon 4)	SNP A/G	Anti-Ro in pSS	Imanishi et al[96]	111/97		
STAT4	Intron 3	Rs7574865	pSS	Korman et al[38]	120/1112		
TAP2	Codon 577	TAP2*Bky2	pSS with anti-Ro	Kumagai et al[71]	108/160	Jean et al[70]	45/200
TCR-βV		Deletion/deletion	pSS	Lawson et al[97]	61/121		
TGF-β1	Codon 10	SNP C/T	pSS with anti-La	Gottenberg et al[98]	129/96		
TNF-α	TNF-α	TNF-α10	pSS with arthritis or anti-Ro	Guggenbuhl et al[69]	35/146	Jean et al[70]	45/200

Src tyrosine kinases (Csk) by which it functions to down-regulate T-cell signaling.[94] Lyp also binds the adaptor molecule, Grb2, leading to the negative regulation of T-cell signaling. In a collection of 70 pSS cases in Columbia and 308 matched controls, Gomez and colleagues[93] found the 1858 T allele a risk factor for SS (OR 2.42). After genotyping a collection of 183 pSS patient samples and 172 healthy controls, however, Ittah and colleagues[94] found no significant difference in the 1858 T allele frequency. Criswell and colleagues[18] also reported no association in their collection of 265 multiplex autoimmune families. The 1858 T allele of PTPN22 is associated with multiple autoimmune diseases, including T1D,[33] RA,[18,32,36,113,114] juvenile idiopathic arthritis,[114,115] SLE,[18,36,41,116] Graves' disease,[37,117] myasthenia gravis,[118] generalized vitiligo,[119] and Wegener's granulomatosis.[120] This allele has been shown to interrupt the interaction of Lyp and Csk, leading to aberrant activation of T cells.[94]

Cytotoxic T-Lymphocyte–Associated Antigen 4

CTLA4 is an important negative regulator of immune responses by T cells. CTLA4 contributes to maintaining peripheral tolerance and acts to suppress T-cell activation and proinflammatory cytokine production.[121] CTLA4 also can trigger apoptosis of activated T cells.[121] In 2006, Downie-Doyle and colleagues[121] genotyped 111 white patients who had pSS and 156 controls and reported association of CTLA4 +49G/A and CT60 haplotypes with susceptibility to pSS. Only months later, Gottenberg and colleagues[122] reported results from two separate cohorts of patients who had pSS and controls. In the first cohort of 142 patients who had pSS and 241 controls, allele frequency differences between patients and controls were observed for the CTLA4 + 49G/A allele (P = .036, OR 1.41) but not CTLA4 CT60. In a second cohort of 139 patients who had pSS, however, an insignificant allelic distribution was observed in CTLA4 + 49G/A and CT60 alleles between patients who had pSS and controls.[122] Inconsistencies between studies in part may be the result of analytic differences between haplotype versus single SNP analyses. The +49A:CT60G haplotype also has been associated with SLE; however, association with additional haplotypes also has been observed but remains to be fully defined.[123,124]

Mannose-Binding Lectin

Mannose-binding lectin (MBL), a serum protein, is critical for host recognition of microorganisms. MBL contains a domain that can bind to the receptor collectin on the surface of phagocytes aiding in the phagocytosis of microorganism.[92] Another important function of MBL is to mediate the activation of the complement pathway by lectin.[92] A mutation in codon 54 of the MBL gene, in addition to other MBL polymorphisms, affects serum levels.[89] Using a collection of 104 cases of pSS in Japan and 143 healthy controls, Wang and colleagues[89] reported a higher allele frequency of wild-type MBL codon 54 in patients who had pSS than in controls (P = .011). Tsutsumi and colleagues[92] found homozygosity for the codon 54 mutation associated with pSS in a separate cohort of Japanese pSS cases and controls. Neither Mullighan[90] nor Aittoniemi[91] could confirm association between MBL polymorphisms and pSS.

FAS and Fas Ligand

FAS and FAS ligand (TNF receptor superfamily, member 6) have been implicated in the pathogenesis of various diseases of the immune system, including SS. These molecules are found on the cell surface and are responsible for transducing a death signal into the cytoplasm, leading to apoptosis.[74] Bolstad and colleagues,[74] upon genotyping a collection of 70 patients who had pSS and 72 healthy controls, observed significant differences in frequencies of three FAS alleles in patients compared with

controls. Mullighan and colleagues,[75] however, did not find FAS alleles associated with SS in their collection of 108 cases and 101 controls.

Ro52

The anti-Ro52 autoantibody was discovered and demonstrated to be present in SS by Ben-Chetrit and colleagues.[125] A polymorphism in intron 1 of the Ro52 autoantigen also was shown associated with SS by Nakken and colleagues[95] in 97 patients who had pSS and were positive for anti-Ro/SSA compared with 72 healthy controls. Similarly, Imanishi and colleagues[96] reported a 7216A/G polymorphism in intron 3 that may influence the presence of anti-SSA/Ro52 antibody in patients who had pSS.

Immunoglobulin KM

Allotypes, originally defined by allospecific sera, are heritable differences in antibody structure and may contribute to genetic risk. In 1984, Whittingham and colleagues[86] discovered an association of anti-La/SSB autoantibodies with KM1 allotype in pSS. Twenty years passed before this discovery was replicated. Pertovaara and colleagues[126] found that anti-La/SSB autoantibodies occurred more frequently in patients who had pSS and the KM(1) allele than in those who did not have the allele ($P = .016$). No associations were observed between specific KM alleles and pSS or within anti-La/SSB subsets of patients who had SS in another study of comparable sample size.[87]

Other Associations

Other associations have been reported with pSS but have yet to be replicated (see **Table 3**). Upon genotyping a collection of 39 patients who had SS and 76 healthy controls, Petrek and colleagues[73] reported that polymorphisms of chemokine (C-C motif) receptor 5 (CCR5) may play a protective role in the development of SS. They found that the frequency of CCR5-delta 32/genotype was lower in patients than in controls.[73] Glutathione S-transferase (GST) MI and GSTT1 genes were investigated for association with SS in 106 Japanese cases and 143 healthy controls. These studies showed that 57.5% of patients who had SS shared the GSTM1 homozygous null genotype compared with 44.1% of controls ($P = .035$). In addition, patients who had SS who shared the GSTM1 genotype were found to have higher levels of anti-Ro/SSA autoantibodies ($P = .0013$).[76] In a study of 63 white Finnish patients who had pSS and 64 healthy controls, the apolipoprotein E (ApoE) $\varepsilon 4$ allele was found associated with early onset of pSS ($P = .047$).[72] Little is known about the function of minor histocompatibility antigen (HA-1). Harangi and colleagues[77] examined three white populations of patients who had pSS and healthy controls and determined that the HA-1 168 His allele frequency was lower in patients who had pSS than in controls ($P < .003$). Finally, Lawson and colleagues[97] observed a decreased frequency of the deleted/deleted genotype of the T-cell receptor beta variable (TCRβV) gene in patients who had pSS compared with controls.

EXPRESSION PROFILING

Developments in high-throughput transcriptional profiling using microarray technology have dramatically enhanced the ability to characterize comprehensive patterns of gene expression in isolated cells from normal and diseased tissues. Gene expression profiling data in patients who have SLE and RA have demonstrated characteristic peripheral blood cell gene expression fingerprints or ''signatures.'' A prominent

signature that has been observed repeatedly in autoimmune phenotypes is marked by overexpression of IFN-inducible genes.[21]

Several gene expression profiling studies in human SS have been reported and thus far have focused on salivary gland tissue and saliva. In a study by Hjelmervik and colleagues,[127] 10 patients who had pSS and 10 controls who had symptoms of SS but no objective criteria were evaluated. RNA was extracted from minor salivary gland tissue and hybridized to cDNA microarrays with features representing approximately 16,000 transcripts. Out of the top 200 most differentially expressed genes, the highest ranked transcripts were from the T-cell receptor β locus and many other genes indicating a chronic inflammatory state. Genes involved in IFN responses, such as increased expression of HLA class I and II and chemokines (eg, CXCL13) that attract lymphocytes to sites of inflammation, also were noted. In addition, down-regulation of the expression of carbonic anhydrase II, essential in saliva production and secretion, also was found, suggesting direct functional abnormalities in SS.

Using a similar study design, Gottenberg and colleagues[128] evaluated minor salivary gland tissue from seven patients who had pSS and seven controls using microarrays containing more than 10,000 probes. Analysis of these data also indicated IFN-mediated innate immune mechanisms in the pathogenesis of pSS. Specifically, 23 genes known to play a role in IFN signaling were identified, including two TLRs, TLR8 and TLR9. This study also demonstrated that plasmacytoid dendritic cells, a major producer of IFN, could be detected by immunohistochemistry in all patients who had SS but none of the controls. More recently, IFN-related gene expression patterns were reported in a third study of three pSS patients and three controls.[129] Furthermore, microarray studies by Hu and colleagues[130] have shown activation of IFN-related pathways is detectable in saliva. A proposed model suggests that stimulation of TLRs (eg, by viral or immune complexes) in salivary glands and downstream signaling pathways may be dysregulated, possibly because of genetic variants that predispose to SS, and that continual stimulation contributes to the persistence of what is observed as the IFN signature.[128] These studies strongly support the role of innate immunity, in addition to adaptive immune mechanisms, in the pathogenesis of SS. Additional studies using similar microarray technologies in saliva and peripheral blood is an area of ongoing work, and holds significant promise for development of biomarkers for improved diagnostic and therapeutic approaches to SS.

MOUSE MODELS

Animal models that resemble pSS are used to evaluate etiology and pathogenesis of SS. Several models have provided some insight into potential genetic contribution to clinical manifestations of the disease and are reviewed in detail elsewhere.[131] To date, there is no single mouse model that fully recapitulates the majority of cardinal disease manifestations of human disease. A large proportion of the approximately 20 models available, however, develop sialoadenitis or dacryoadenitis, so these models are particularly valuable tools for evaluating initiation of disease, various components of the overall SS phenotype, and the effects of immune manipulation. Those models that have been most characterized thoroughly or seem especially promising and for which genetic information is available that may aid in understanding human disease are highlighted.

The nonobese diabetic (NOD) mouse is an inbred strain that has been established as a model to study autoimmune T1D.[132] At 16 weeks of age, NOD mice spontaneously develop sialoadenitis and glandular dysfunction unrelated to the development of diabetes.[133] Diabetes and sialoadenitis develop independently in the NOD mouse. Various autoantibodies have been found in NOD mice, including those to alpha-fodrin,

antinuclear antibodies (anti-Ro/SSA and anti-La/SSB), and antibodies to M3 muscarinic acetylcholine receptor.[134] Two genetic regions, Aec2 and Aec1, are essential for the development of SS-like disease; however, the precise gene/locus conferring risk is undefined.[131] NOD mice also carry a unique MHC haplotype ($H2^{g7}$) that is permissive for development of disease.

Several mouse models seem suitable for studying SS secondary to SLE.[131,135] The MRL/lpr strain carries a mutation in the lpr gene that impairs FAS expression, leading to apoptotic resistance in T cells. Mice develop B-cell hyper-reactivity, produce autoantibodies, and exhibit destruction of glandular tissue with loss of secretory function.[131] The NZB/W F1 mouse, also originally used as a model for human SLE, presents inflammatory infiltrates composed primarily of CD4+ T cells and some B and CD8+ T cells.[136,137] An increase in periductal laminin expression in the submandibular salivary gland of NZB/W F1 mice may result in the development of sialoadenitis.[138] Transgenic and knockout mice for TGF-β1, BAFF, and IL-14α also develop phenotypes with features of SLE and SS.[131]

Mouse models that seem to manifest phenotypes more reminiscent of pSS have been reported. In 1997, Saegusa and Kubota established the IQI/Jic mouse as a model for pSS. By 2 months of age, these mice develop infiltrating lymphocytes consisting of CD4+ T cells in small foci and B cells in large foci of the salivary glands.[139] Recent studies have suggested that expression of a tissue kallikrein 13 (klk-13) autoantigen in salivary glands may contribute to development of sialoadenitis in the IQI/Jic model.[140] Similarly, the NFS/sld mouse develops sialoadenitis that is characterized by inflammatory lesions containing CD3+ and CD4+ cells with few CD8+ and B cells. The mice carry an autosomal recessive gene, sld, and autoimmunity seems driven by reactivity against the cytoskeletal protein α-fodrin.[141,142] No anti-Ro/SSA or anti-La/SSB are detected, however, in the NFS/sld model.[143] Another model, the aly/aly mouse, carries an autosomal recessive alymphoplasia (aly) mutation mapped to a gene that codes for a nuclear factor κB–inducing kinase.[144] CD4+ T cells infiltrate the lacrimal and salivary glands at 3 months.[145] The major deficiency of the Aly/aly mouse is the lack of autoantibodies against nuclear elements or salivary glands, inconsistent with the serology of most human patients who had pSS.

Three promising new models for pSS include the Id3 knockout mouse and two inducible models. First, Id3 is a gene involved in T-cell receptor-mediated thymic selection at the time of T-cell development. Mice deficient in Id3 develop anti-Ro/SSA and anti-La/SSB antibodies and dry eyes and mouth and experience lymphocyte infiltration in lachrymal and salivary glands.[146] After application of a CD20 monoclonal antibody treatment to Id3 knockouts, Id3 mice experienced sustained B lymphocyte loss. Recovery of salivary function and improvements of histopathology were observed.[147] Perhaps the Id3 knockout model for immunotherapy will translate successfully in patients who have pSS. Second, Fleck and colleagues[148] infected the C57BL/6-*lpr/lpr* mouse with murine cytomegalovirus and reported the development of acute and chronic sialadenitis. The persistence of salivary gland inflammation and high levels of anti-Ro/SSA and anti-La/SSB production resemble SS.[148] Finally, in 2005, Scofield and colleagues[149] introduced the BALB/c mouse immunized with Ro274 or Ro480 peptides from the Ro/SSA autoantigen. They reported the presence of infiltrating lymphocytes in these mice, reduced saliva production, and high-titer anti-Ro/SSA and anti-La/SSB.[149] The characteristics of this model most closely resemble pSS disease in humans. As with the majority of mouse models described for SS, dissection of the genetic loci that drive lymphocytic infiltration, aberrant cytokine production, development of autoantibodies, and glandular dysfunction will provide important tools for understanding human disease. Likewise, identification of causal genes in humans is

necessary to fully inform the development of mouse models that more accurately represents human disease.

SUMMARY

The evidence for a strong genetic component conferring susceptibility to pSS is mounting. Several associations with SS have been reported to date and provide evidence that the HLA region harbors important susceptibility loci and that multiple genes outside the HLA region play a role. Genetic discovery in SS, however, lags far behind the astounding success recently observed in other closely related autoimmune diseases. Full leveraging of the power of genome-wide association studies and other state-of-the-art genetic and genomic tools for discovery and replication of genetic factors in SS undoubtedly will require investigators to build large cohorts of well characterized patients. Genes involved in T- and B-cell function and innate immune mechanisms, such as IFN signaling, cytokine levels, and expression of autoantigens, all are likely important. Identifying the genetic factors that cause SS should provide fundamental new knowledge about this complex disease, allowing for more precise definition of pathogenic mechanisms leading to the overall SS phenotype and clinically heterogeneous subsets of patients. Critical opportunities are certain to follow for rapid translation into improved diagnosis and therapies for SS and its spectrum diseases.

REFERENCES

1. Bolstad AI, Jonsson R. Genetic aspects of Sjogren's syndrome. Arthritis Res 2002;4(6):353–9.
2. Bowman SJ, Ibrahim GH, Holmes G, et al. Estimating the prevalence among Caucasian women of primary Sjogren's syndrome in two general practices in Birmingham, UK. Scand J Rheumatol 2004;33(1):39–43.
3. Dafni UG, Tzioufas AG, Staikos P, et al. Prevalence of Sjogren's syndrome in a closed rural community. Ann Rheum Dis 1997;56(9):521–5.
4. Haugen AJ, Peen E, Hulten B, et al. Estimation of the prevalence of primary Sjogren's syndrome in two age-different community-based populations using two sets of classification criteria: the Hordaland Health Study. Scand J Rheumatol 2008;37(1):30–4.
5. Manthorpe R, Frost-Larsen K, Isager H, et al. Sjogren's syndrome. A review with emphasis on immunological features. Allergy 1981;36(3):139–53.
6. Sanchez-Guerrero J, Perez-Dosal MR, Cardenas-Velazquez F, et al. Prevalence of Sjogren's syndrome in ambulatory patients according to the American-European Consensus Group criteria. Rheumatology (Oxford) 2005;44(2):235–40.
7. Besana C, Salmaggi C, Pellegrino C, et al. Chronic bilateral dacryo-adenitis in identical twins: a possible incomplete form of Sjogren syndrome. Eur J Pediatr 1991;150(9):652–5.
8. Bolstad AI, Haga HJ, Wassmuth R, et al. Monozygotic twins with primary Sjogren's syndrome. J Rheumatol 2000;27(9):2264–6.
9. Houghton KM, Cabral DA, Petty RE, et al. Primary Sjogren's syndrome in dizygotic adolescent twins: one case with lymphocytic interstitial pneumonia. J Rheumatol 2005;32(8):1603–6.
10. Scofield RH, Kurien BT, Reichlin M. Immunologically restricted and inhibitory anti-Ro/SSA in monozygotic twins. Lupus 1997;6(4):395–8.
11. Boling EP, Wen J, Reveille JD, et al. Primary Sjogren's syndrome and autoimmune hemolytic anemia in sisters. A family study. Am J Med 1983;74(6): 1066–71.

12. Lichtenfeld JL, Kirschner RH, Wiernik PH. Familial Sjogren's syndrome with associated primary salivary gland lymphoma. Am J Med 1976;60(2):286–92.
13. Mason AM, Golding PL. Multiple immunological abnormalities in a family. J Clin Pathol 1971;24(8):732–5.
14. Reveille JD. The molecular genetics of systemic lupus erythematosus and Sjogren's syndrome. Curr Opin Rheumatol 1992;4(5):644–56.
15. Sabio JM, Milla E, Jimenez-Alonso J. A multicase family with primary Sjogren's syndrome. J Rheumatol 2001;28(8):1932–4.
16. Sestak AL, Shaver TS, Moser KL, et al. Familial aggregation of lupus and autoimmunity in an unusual multiplex pedigree. J Rheumatol 1999;26(7):1495–9.
17. Reveille JD, Wilson RW, Provost TT, et al. Primary Sjogren's syndrome and other autoimmune diseases in families. Prevalence and immunogenetic studies in six kindreds. Ann Intern Med 1984;101(6):748–56.
18. Criswell LA, Pfeiffer KA, Lum RF, et al. Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. Am J Hum Genet 2005; 76(4):561–71.
19. Giles I, Isenberg D. Fatigue in primary Sjogren's syndrome: is there a link with the fibromyalgia syndrome? Ann Rheum Dis 2000;59(11):875–8.
20. Fox RP. Head and neck findings in systemic lupus erythematosus: Sjogren's syndrome and the eye, ear, and larynx. Philadelphia: Lippencott, Williams, Wilkins; 2008.
21. Baechler EC, Batliwalla FM, Reed AM, et al. Gene expression profiling in human autoimmunity. Immunol Rev 2006;210:120–37.
22. Graham RR, Ortmann WA, Langefeld CD, et al. Visualizing human leukocyte antigen class II risk haplotypes in human systemic lupus erythematosus. Am J Hum Genet 2002;71(3):543–53.
23. Barreto M, Santos E, Ferreira R, et al. Evidence for CTLA4 as a susceptibility gene for systemic lupus erythematosus. Eur J Hum Genet 2004;12(8):620–6.
24. Blomhoff A, Kemp EH, Gawkrodger DJ, et al. CTLA4 polymorphisms are associated with vitiligo, in patients with concomitant autoimmune diseases. Pigment Cell Res 2005;18(1):55–8.
25. Blomhoff A, Lie BA, Myhre AG, et al. Polymorphisms in the cytotoxic T lymphocyte antigen-4 gene region confer susceptibility to Addison's disease. J Clin Endocrinol Metab 2004;89(7):3474–6.
26. Furugaki K, Shirasawa S, Ishikawa N, et al. Association of the T-cell regulatory gene CTLA4 with Graves' disease and autoimmune thyroid disease in the Japanese. J Hum Genet 2004;49(3):166–8.
27. Hunt KA, McGovern DP, Kumar PJ, et al. A common CTLA4 haplotype associated with coeliac disease. Eur J Hum Genet 2005;13(4):440–4.
28. Lee CS, Lee YJ, Liu HF, et al. Association of CTLA4 gene A-G polymorphism with rheumatoid arthritis in Chinese. Clin Rheumatol 2003;22(3):221–4.
29. Torres B, Aguilar F, Franco E, et al. Association of the CT60 marker of the CTLA4 gene with systemic lupus erythematosus. Arthritis Rheum 2004;50(7):2211–5.
30. Zhou Y, Huang D, Paris PL, et al. An analysis of CTLA-4 and proinflammatory cytokine genes in Wegener's granulomatosis. Arthritis Rheum 2004;50(8): 2645–50.
31. Prokunina L, Alarcon-Riquelme M. The genetic basis of systemic lupus erythematosus—knowledge of today and thoughts for tomorrow. Hum Mol Genet 2004;13(Spec No 1):R143–8.

32. Begovich AB, Carlton VE, Honigberg LA, et al. A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. Am J Hum Genet 2004;75(2):330–7.
33. Bottini N, Musumeci L, Alonso A, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type 1 diabetes. Nat Genet 2004;36(4):337–8.
34. Ladner MB, Bottini N, Valdes AM, et al. Association of the single nucleotide polymorphism C1858T of the PTPN22 gene with type 1 diabetes. Hum Immunol 2005;66(1):60–4.
35. Onengut-Gumuscu S, Ewens KG, Spielman RS, et al. A functional polymorphism (1858C/T) in the PTPN22 gene is linked and associated with type 1 diabetes in multiplex families. Genes Immun 2004;5(8):678–80.
36. Orozco G, Sanchez E, Gonzalez-Gay MA, et al. Association of a functional single-nucleotide polymorphism of PTPN22, encoding lymphoid protein phosphatase, with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Rheum 2005;52(1):219–24.
37. Velaga MR, Wilson V, Jennings CE, et al. The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves' disease. J Clin Endocrinol Metab 2004;89(11):5862–5.
38. Korman BD, Alba MI, Le JM, et al. Variant form of STAT4 is associated with primary Sjogren's syndrome. Genes Immun 2008;9(3):267–70.
39. Marrack P, Kappler J, Kotzin BL. Autoimmune disease: why and where it occurs. Nat Med 2001;7(8):899–905.
40. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447(7148):1087–93.
41. Harley JB, Alarcon-Riquelme ME, Criswell LA, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet 2008;40(2):204–10.
42. Hom G, Graham RR, Modrek B, et al. Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. N Engl J Med 2008;358(9):900–9.
43. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet 2008; 9(5):356–69.
44. Todd JA, Walker NM, Cooper JD, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet 2007; 39(7):857–64.
45. Wellcome-Trust-Case-Control-Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447(7145):661–78.
46. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61(6):554–8.
47. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjogren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36(3):340–7.
48. Locht H, Pelck R, Manthorpe R. Clinical manifestations correlated to the prevalence of autoantibodies in a large (n = 321) cohort of patients with primary Sjogren's syndrome: a comparison of patients initially diagnosed according to the Copenhagen classification criteria with the American-European consensus criteria. Autoimmun Rev 2005;4(5):276–81.
49. Complete sequence and gene map of a human major histocompatibility complex. The MHC sequencing consortium. Nature 1999;401(6756):921–3.

50. Merriman TR, Todd JA. Genetics of autoimmune disease. Curr Opin Immunol 1995;7(6):786–92.
51. Nepom GT. MHC and autoimmune diseases. Immunol Ser 1993;59:143–64.
52. Chused TM, Kassan SS, Opelz G, et al. Sjogren's syndrome association with HLA-Dw3. N Engl J Med 1977;296(16):895–7.
53. Fye KH, Terasaki PI, Michalski JP, et al. Relationshipp of HLA-Dw3 and HLA-B8 to Sjogren's syndrome. Arthritis Rheum 1978;21(3):337–42.
54. Manthorpe R, Morling N, Platz P, et al. HLA-D antigen frequencies in Sjogren's syndrome. Differences between the primary and secondary form. Scand J Rheumatol 1981;10(2):124–8.
55. Anaya JM, Mantilla RD, Correa PA. Immunogenetics of primary Sjogren's syndrome in Colombians. Semin Arthritis Rheum 2005;34(5):735–43.
56. Guggenbuhl P, Jean S, Jego P, et al. Primary Sjogren's syndrome: role of the HLA-DRB1*0301-*1501 heterozygotes. J Rheumatol 1998;25(5):900–5.
57. Mattey DL, Gonzalez-Gay MA, Hajeer AH, et al. Association between HLA-DRB1*15 and secondary Sjogren's syndrome in patients with rheumatoid arthritis. J Rheumatol 2000;27(11):2611–6.
58. Nakken B, Jonsson R, Brokstad KA, et al. Associations of MHC class II alleles in Norwegian primary Sjogren's syndrome patients: implications for development of autoantibodies to the Ro52 autoantigen. Scand J Immunol 2001;54(4):428–33.
59. Bolstad AI, Wassmuth R, Haga HJ, et al. HLA markers and clinical characteristics in Caucasians with primary Sjogren's syndrome. J Rheumatol 2001;28(7): 1554–62.
60. Kang HI, Fei HM, Saito I, et al. Comparison of HLA class II genes in Caucasoid, Chinese, and Japanese patients with primary Sjogren's syndrome. J Immunol 1993;150(8 Pt 1):3615–23.
61. Rischmueller M, Lester S, Chen Z, et al. HLA class II phenotype controls diversification of the autoantibody response in primary Sjogren's syndrome (pSS). Clin Exp Immunol 1998;111(2):365–71.
62. Miyagawa S, Shinohara K, Nakajima M, et al. Polymorphisms of HLA class II genes and autoimmune responses to Ro/SS-A-La/SS-B among Japanese subjects. Arthritis Rheum 1998;41(5):927–34.
63. Scofield RH, Frank MB, Neas BR, et al. Cooperative association of T cell beta receptor and HLA-DQ alleles in the production of anti-Ro in systemic lupus erythematosus. Clin Immunol Immunopathol 1994;72(3):335–41.
64. Hadj Kacem H, Kaddour N, Adyel FZ, et al. TNFa IR2/IR4 and CTLA-4 polymorphisms in Tunisian patients with rheumatoid arthritis and Sjogren's syndrome. Rheumatology (Oxford) 2001;40(12):1370–4.
65. Harley JB, Reichlin M, Arnett FC, et al. Gene interaction at HLA-DQ enhances autoantibody production in primary Sjogren's syndrome. Science 1986; 232(4754):1145–7.
66. Gershwin ME, Terasaki I, Graw R, et al. Increased frequency of HL-A8 in Sjogren's syndrome. Tissue Antigens 1975;6(5):342–6.
67. Ivanyi D, Drizhal I, Erbenova E, et al. HL-A in Sjogren's syndrome. Tissue Antigens 1976;7(1):45–51.
68. Loiseau P, Lepage V, Djelal F, et al. HLA class I and class II are both associated with the genetic predisposition to primary Sjogren syndrome. Hum Immunol 2001;62(7):725–31.
69. Guggenbuhl P, Veillard E, Quelvenec E, et al. Analysis of TNFalpha microsatellites in 35 patients with primary Sjogren's syndrome. Joint Bone Spine 2000; 67(4):290–5.

70. Jean S, Quelvennec E, Alizadeh M, et al. DRB1*15 and DRB1*03 extended haplotype interaction in primary Sjogren's syndrome genetic susceptibility. Clin Exp Rheumatol 1998;16(6):725–8.
71. Kumagai S, Kanagawa S, Morinobu A, et al. Association of a new allele of the TAP2 gene, TAP2*Bky2 (Val577), with susceptibility to Sjogren's syndrome. Arthritis Rheum 1997;40(9):1685–92.
72. Pertovaara M, Lehtimaki T, Rontu R, et al. Presence of apolipoprotein E epsilon4 allele predisposes to early onset of primary Sjogren's syndrome. Rheumatology (Oxford) 2004;43(12):1484–7.
73. Petrek M, Cermakova Z, Hutyrova B, et al. CC chemokine receptor 5 and interleukin-1 receptor antagonist gene polymorphisms in patients with primary Sjogren's syndrome. Clin Exp Rheumatol 2002;20(5):701–3.
74. Bolstad AI, Wargelius A, Nakken B, et al. Fas and Fas ligand gene polymorphisms in primary Sjogren's syndrome. J Rheumatol 2000;27(10): 2397–405.
75. Mullighan CG, Heatley S, Lester S, et al. Fas gene promoter polymorphisms in primary Sjogren's syndrome. Ann Rheum Dis 2004;63(1):98–101.
76. Morinobu A, Kanagawa S, Koshiba M, et al. Association of the glutathione S-transferase M1 homozygous null genotype with susceptibility to Sjogren's syndrome in Japanese individuals. Arthritis Rheum 1999;42(12):2612–5.
77. Harangi M, Kaminski WE, Fleck M, et al. Homozygosity for the 168His variant of the minor histocompatibility antigen HA-1 is associated with reduced risk of primary Sjogren's syndrome. Eur J Immunol 2005;35(1):305–17.
78. Perrier S, Coussediere C, Dubost JJ, et al. IL-1 receptor antagonist (IL-1RA) gene polymorphism in Sjogren's syndrome and rheumatoid arthritis. Clin Immunol Immunopathol 1998;87(3):309–13.
79. Youn J, Hwang SH, Cho CS, et al. Association of the interleukin-4 receptor alpha variant Q576R with Th1/Th2 imbalance in connective tissue disease. Immunogenetics 2000;51(8-9):743–6.
80. Lester S, Downie-Doyle S, Gordon TP, et al. The IL4-Ra Q57^R polymorphism is not associated with primary Sjorgren''s syndrome. Arthritis Rheum 2000; 43(Suppl):s304.
81. Ramos-Casals M, Font J, Brito-Zeron P, et al. Interleukin-4 receptor alpha polymorphisms in primary Sjogren's syndrome. Clin Exp Rheumatol 2004; 22(3):374.
82. Hulkkonen J, Pertovaara M, Antonen J, et al. Elevated interleukin-6 plasma levels are regulated by the promoter region polymorphism of the IL6 gene in primary Sjogren's syndrome and correlate with the clinical manifestations of the disease. Rheumatology (Oxford) 2001;40(6):656–61.
83. Limaye V, Lester S, Downie-Doyle S, et al. Polymorphisms of the interleukin 10 gene promoter are not associated with anti-Ro autoantibodies in primary Sjogren's syndrome. J Rheumatol 2000;27(12):2945–6.
84. Origuchi T, Kawasaki E, Ide A, et al. Correlation between interleukin 10 gene promoter region polymorphisms and clinical manifestations in Japanese patients with Sjogren's syndrome. Ann Rheum Dis 2003;62(11):1117–8.
85. Font J, Garcia-Carrasco M, Ramos-Casals M, et al. The role of interleukin-10 promoter polymorphisms in the clinical expression of primary Sjogren's syndrome. Rheumatology (Oxford) 2002;41(9):1025–30.
86. Whittingham S, Propert DN, Mackay IR. A strong association between the antinuclear antibody anti-La (SS-B) and the kappa chain allotype Km(1). Immunogenetics 1984;19(4):295–9.

87. Downie-Doyle S, Lester S, Bardy P, et al. Immunoglobulin kappa light chain gene alleles are not associated with primary Sjogren's syndrome. Genes Immun 2002; 3(Suppl 1):S63–5.
88. Miceli-Richard C, Comets E, Loiseau P, et al. Association of an IRF5 gene functional polymorphism with Sjogren's syndrome. Arthritis Rheum 2007;56(12): 3989–94.
89. Wang ZY, Morinobu A, Kanagawa S, et al. Polymorphisms of the mannose binding lectin gene in patients with Sjogren's syndrome. Ann Rheum Dis 2001;60(5):483–6.
90. Mullighan CG, Heatley S, Bardy PG, et al. Lack of association between mannose-binding lectin gene polymorphisms and primary Sjogren's syndrome. Arthritis Rheum 2000;43(12):2851–2.
91. Aittoniemi J, Pertovaara M, Hulkkonen J, et al. The significance of mannan-binding lectin gene alleles in patients with primary Sjogren's syndrome. Scand J Rheumatol 2002;31(6):362–5.
92. Tsutsumi A, Sasaki K, Wakamiya N, et al. Mannose-binding lectin gene: polymorphisms in Japanese patients with systemic lupus erythematosus, rheumatoid arthritis and Sjogren's syndrome. Genes Immun 2001;2(2):99–104.
93. Gomez LM, Anaya JM, Gonzalez CI, et al. PTPN22 C1858T polymorphism in Colombian patients with autoimmune diseases. Genes Immun 2005;6(7):628–31.
94. Ittah M, Gottenberg JE, Proust A, et al. No evidence for association between 1858 C/T single-nucleotide polymorphism of PTPN22 gene and primary Sjogren's syndrome. Genes Immun 2005;6(5):457–8.
95. Nakken B, Jonsson R, Bolstad AI. Polymorphisms of the Ro52 gene associated with anti-Ro 52-kd autoantibodies in patients with primary Sjogren's syndrome. Arthritis Rheum 2001;44(3):638–46.
96. Imanishi T, Morinobu A, Hayashi N, et al. A novel polymorphism of the SSA1 gene is associated with anti-SS-A/Ro52 autoantibody in Japanese patients with primary Sjogren's syndrome. Clin Exp Rheumatol 2005;23(4):521–4.
97. Lawson CA, Donaldson IJ, Bowman SJ, et al. Analysis of the insertion/deletion related polymorphism within T cell antigen receptor beta variable genes in primary Sjogren's syndrome. Ann Rheum Dis 2005;64(3):468–70.
98. Gottenberg JE, Busson M, Loiseau P, et al. Association of transforming growth factor beta1 and tumor necrosis factor alpha polymorphisms with anti-SSB/La antibody secretion in patients with primary Sjogren's syndrome. Arthritis Rheum 2004;50(2):570–80.
99. Hulkkonen J, Pertovaara M, Antonen J, et al. Genetic association between interleukin-10 promoter region polymorphisms and primary Sjogren's syndrome. Arthritis Rheum 2001;44(1):176–9.
100. Morinobu A, Gadina M, Strober W, et al. STAT4 serine phosphorylation is critical for IL-12-induced IFN-gamma production but not for cell proliferation. Proc Natl Acad Sci U S A 2002;99(19):12281–6.
101. Nishikomori R, Usui T, Wu CY, et al. Activated STAT4 has an essential role in Th1 differentiation and proliferation that is independent of its role in the maintenance of IL-12R beta 2 chain expression and signaling. J Immunol 2002;169(8): 4388–98.
102. Remmers EF, Plenge RM, Lee AT, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. N Engl J Med 2007;357(10):977–86.
103. Takaoka A, Yanai H, Kondo S, et al. Integral role of IRF-5 in the gene induction programme activated by Toll-like receptors. Nature 2005;434(7030):243–9.
104. Taniguchi T, Ogasawara K, Takaoka A, et al. IRF family of transcription factors as regulators of host defense. Annu Rev Immunol 2001;19:623–55.

105. Graham RR, Kyogoku C, Sigurdsson S, et al. Three functional variants of IFN regulatory factor 5 (IRF5) define risk and protective haplotypes for human lupus. Proc Natl Acad Sci U S A 2007;104(16):6758–63.
106. Demirci FY, Manzi S, Ramsey-Goldman R, et al. Association of a common interferon regulatory factor 5 (IRF5) variant with increased risk of systemic lupus erythematosus (SLE). Ann Hum Genet 2007;71(Pt 3):308–11.
107. Graham RR, Kozyrev SV, Baechler EC, et al. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. Nat Genet 2006;38(5): 550–5.
108. Kelly JA, Kelley JM, Kaufman KM, et al. Interferon regulatory factor-5 is genetically associated with systemic lupus erythematosus in African Americans. Genes Immun 2008;9(3):187–94.
109. Kozyrev SV, Lewen S, Reddy PM, et al. Structural insertion/deletion variation in IRF5 is associated with a risk haplotype and defines the precise IRF5 isoforms expressed in systemic lupus erythematosus. Arthritis Rheum 2007;56(4): 1234–41.
110. Reddy MV, Velazquez-Cruz R, Baca V, et al. Genetic association of IRF5 with SLE in Mexicans: higher frequency of the risk haplotype and its homozygozity than Europeans. Hum Genet 2007;121(6):721–7.
111. Shin HD, Sung YK, Choi CB, et al. Replication of the genetic effects of IFN regulatory factor 5 (IRF5) on systemic lupus erythematosus in a Korean population. Arthritis Res Ther 2007;9(2):R32.
112. Sigurdsson S, Nordmark G, Goring HH, et al. Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. Am J Hum Genet 2005;76(3):528–37.
113. Lee AT, Li W, Liew A, et al. The PTPN22 R620W polymorphism associates with RF positive rheumatoid arthritis in a dose-dependent manner but not with HLA-SE status. Genes Immun 2005;6(2):129–33.
114. Viken MK, Amundsen SS, Kvien TK, et al. Association analysis of the 1858C > T polymorphism in the PTPN22 gene in juvenile idiopathic arthritis and other autoimmune diseases. Genes Immun 2005;6(3):271–3.
115. Hinks A, Barton A, John S, et al. Association between the PTPN22 gene and rheumatoid arthritis and juvenile idiopathic arthritis in a UK population: further support that PTPN22 is an autoimmunity gene. Arthritis Rheum 2005;52(6): 1694–9.
116. Kyogoku C, Langefeld CD, Ortmann WA, et al. Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. Am J Hum Genet 2004;75(3):504–7.
117. Smyth D, Cooper JD, Collins JE, et al. Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general autoimmunity locus. Diabetes 2004;53(11): 3020–3.
118. Vandiedonck C, Capdevielle C, Giraud M, et al. Association of the PTPN22*R620W polymorphism with autoimmune myasthenia gravis. Ann Neurol 2006;59(2):404–7.
119. Canton I, Akhtar S, Gavalas NG, et al. A single-nucleotide polymorphism in the gene encoding lymphoid protein tyrosine phosphatase (PTPN22) confers susceptibility to generalised vitiligo. Genes Immun 2005;6(7):584–7.
120. Jagiello P, Aries P, Arning L, et al. The PTPN22 620W allele is a risk factor for Wegener's granulomatosis. Arthritis Rheum 2005;52(12):4039–43.

121. Downie-Doyle S, Bayat N, Rischmueller M, et al. Influence of CTLA4 haplotypes on susceptibility and some extraglandular manifestations in primary Sjogren's syndrome. Arthritis Rheum 2006;54(8):2434–40.
122. Gottenberg JE, Loiseau P, Azarian M, et al. CTLA-4 +49A/G and CT60 gene polymorphisms in primary Sjogren syndrome. Arthritis Res Ther 2007; 9(2):R24.
123. Graham DS, Wong AK, McHugh NJ, et al. Evidence for unique association signals in SLE at the CD28-CTLA4-ICOS locus in a family-based study. Hum Mol Genet 2006;15(21):3195–205.
124. Lester S, Downie-Doyle S, Rischmueller M. CTLA4 polymorphism and primary Sjogren's syndrome. Arthritis Res Ther 2007;9(3):401 [author reply 402].
125. Ben-Chetrit E, Chan EK, Sullivan KF, et al. A 52-kD protein is a novel component of the SS-A/Ro antigenic particle. J Exp Med 1988;167(5):1560–71.
126. Pertovaara M, Hurme M, Antonen J, et al. Immunoglobulin KM and GM gene polymorphisms modify the clinical presentation of primary Sjogren's syndrome. J Rheumatol 2004;31(11):2175–80.
127. Hjelmervik TO, Petersen K, Jonassen I, et al. Gene expression profiling of minor salivary glands clearly distinguishes primary Sjogren's syndrome patients from healthy control subjects. Arthritis Rheum 2005;52(5):1534–44.
128. Gottenberg JE, Cagnard N, Lucchesi C, et al. Activation of IFN pathways and plasmacytoid dendritic cell recruitment in target organs of primary Sjogren's syndrome. Proc Natl Acad Sci U S A 2006;103(8):2770–5.
129. Wakamatsu E, Matsumoto I, Yasukochi T, et al. Overexpression of phosphorylated STAT-1alpha in the labial salivary glands of patients with Sjogren's syndrome. Arthritis Rheum 2006;54(11):3476–84.
130. Hu S, Wang J, Meijer J, et al. Salivary proteomic and genomic biomarkers for primary Sjogren's syndrome. Arthritis Rheum 2007;56(11):3588–600.
131. Soyfoo MS, Steinfeld S, Delporte C. Usefulness of mouse models to study the pathogenesis of Sjogren's syndrome. Oral Dis 2007;13(4):366–75.
132. Kikutani H, Makino S. The murine autoimmune diabetes model: NOD and related strains. Adv Immunol 1992;51:285–322.
133. Hu Y, Nakagawa Y, Purushotham KR, et al. Functional changes in salivary glands of autoimmune disease-prone NOD mice. Am J Physiol 1992;263(4 Pt 1): E607–614.
134. Cha S, Peck AB, Humphreys-Beher MG. Progress in understanding autoimmune exocrinopathy using the non-obese diabetic mouse: an update. Crit Rev Oral Biol Med 2002;13(1):5–16.
135. Fujita H, Fujihara T, Takeuchi T, et al. Lacrimation and salivation are not related to lymphocytic infiltration in lacrimal and salivary glands in MRL lpr/lpr mice. Adv Exp Med Biol 1998;438:941–8.
136. Jonsson R, Tarkowski A, Backman K, et al. Immunohistochemical characterization of sialadenitis in NZB X NZW F1 mice. Clin Immunol Immunopathol 1987; 42(1):93–101.
137. Kessler HS. A laboratory model for Sjogren's syndrome. Am J Pathol 1968;52(3): 671–85.
138. Hayashi T, Shirachi T, Hasegawa K. Relationship between sialoadenitis and periductal laminin expression in the submandibular salivary gland of NZBxNZWF(1) mice. J Comp Pathol 2001;125(2–3):110–6.
139. Saegusa J, Kubota H. Sialadenitis in IQI/Jic mice: a new animal model of Sjögren's syndrome. J Vet Med Sci 1997;59(10):897–903.

140. Takada K, Takiguchi M, Konno A, et al. Autoimmunity against a tissue kallikrein in IQI/Jic Mice: a model for Sjogren's syndrome. J Biol Chem 2005;280(5): 3982–8.
141. Hayashi Y, Kojima A, Hata M, et al. A new mutation involving the sublingual gland in NFS/N mice. Partially arrested mucous cell differentiation. Am J Pathol 1988;132(2):187–91.
142. Ishimaru N, Yoneda T, Saegusa K, et al. Severe destructive autoimmune lesions with aging in murine Sjogren's syndrome through Fas-mediated apoptosis. Am J Pathol 2000;156(5):1557–64.
143. Haneji N, Hamano H, Yanagi K, et al. A new animal model for primary Sjogren's syndrome in NFS/sld mutant mice. J Immunol 1994;153(6):2769–77.
144. Shinkura R, Kitada K, Matsuda F, et al. Alymphoplasia is caused by a point mutation in the mouse gene encoding Nf-kappa b-inducing kinase. Nat Genet 1999;22(1):74–7.
145. Tsubata R, Tsubata T, Hiai H, et al. Autoimmune disease of exocrine organs in immunodeficient alymphoplasia mice: a spontaneous model for Sjogren's syndrome. Eur J Immunol 1996;26(11):2742–8.
146. Li H, Dai M, Zhuang Y. A T cell intrinsic role of Id3 in a mouse model for primary Sjogren's syndrome. Immunity 2004;21(4):551–60.
147. Hayakawa I, Tedder TF, Zhuang Y. B-lymphocyte depletion ameliorates Sjogren's syndrome in Id3 knockout mice. Immunology 2007;122(1):73–9.
148. Fleck M, Kern ER, Zhou T, et al. Murine cytomegalovirus induces a Sjogren's syndrome-like disease in C57Bl/6-lpr/lpr mice. Arthritis Rheum 1998;41(12): 2175–84.
149. Scofield RH, Asfa S, Obeso D, et al. Immunization with short peptides from the 60-kDa Ro antigen recapitulates the serological and pathological findings as well as the salivary gland dysfunction of Sjogren's syndrome. J Immunol 2005; 175(12):8409–14.

Hepatitis C Virus and Sjögren's Syndrome: Trigger or Mimic?

Manuel Ramos-Casals, MD, PhD*, Sandra Muñoz, MD,
Pilar Brito Zerón, MD, PhD

KEYWORDS

• Hepatitis C virus • Sjögren syndrome • Cryoglobulinemia
• Lymphoma • Hypocomplementemia

Sjögren's syndrome (SS) is a systemic autoimmune disease that presents with sicca symptomatology of the main mucosa surfaces.[1] The main sicca features (xerophthalmia and xerostomia) are determined by specific ocular (rose Bengal staining, Schirmer test) and oral (salivary flow measurement, parotid scintigraphy) tests. The histologic hallmark is a focal lymphocytic infiltration of the exocrine glands, determined by a biopsy of the minor labial salivary glands.[2] Patients with SS present a broad spectrum of analytic features (cytopenias, hypergammaglobulinemia, high erythrocyte sedimentation rate) and autoantibodies, of which antinuclear antibodies (ANA) are the most frequently detected, anti–Ro/SS-A the most specific, and cryoglobulins and hypocomplementemia the main prognostic markers.[3] The disease spectrum extends from sicca syndrome to systemic involvement (extraglandular manifestations).[4]

Autoimmunity and viral infections are closely related fields, and viruses have been proposed as possible etiologic or triggering agents of systemic autoimmune diseases. In recent decades, many research groups have focused on the role of viral infection in the etiopathogenesis of SS. The main candidates are herpesviruses, such as Epstein-Barr virus, and cytomegalovirus, which have a high seroprevalence in the general population, with more than 90% of adults presenting IgG against these viruses. Recent studies have suggested, however, that the hepatitis C virus (HCV) should also be considered as a potential pathogenic agent in SS.

HEPATITIS C VIRUS IN SJÖGREN'S SYNDROME PATIENTS: TRIGGER OR MIMIC?

HCV, a linear, single-stranded RNA virus identified in 1989,[5] is recognized as one of the viruses most often associated with autoimmune features and the extrahepatic

Supported by Grant FIS 04/0701.
Laboratory of Autoimmune Diseases "Josep Font," IDIBAPS, Department of Autoimmune Diseases, C/Villaroel 170, Hospital Clinic, Barcelona 08036, Spain
* Corresponding author.
E-mail address: mramos@clinic.ub.es (M. Ramos-Casals).

Rheum Dis Clin N Am 34 (2008) 869–884
doi:10.1016/j.rdc.2008.08.007 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

manifestations often observed in patients with chronic HCV infection, both clinical and immunologic (**Table 1**),[6] may lead to the fulfillment of the current classification criteria for some systemic autoimmune diseases (**Table 2**).[7] In 1992, Haddad and colleagues[8] found histologic evidence of SS (Chisholm-Mason classification grade 3 or 4) in 16 of 28 patients with chronic HCV infection. Since then more than 400 cases of SS-HCV have been reported, making SS one of the systemic autoimmune disease most closely associated with HCV.[9] In addition, SS is the systemic autoimmune disease with the highest prevalence of chronic HCV infection, which has been detected in 156 (12%) of 1309 SS patients tested by ELISA.[10] The association of SS with HCV has originated an intense debate, however, and it is not established whether this is a virus-induced disease mimicking primary SS or whether it is a true etiopathogenic subset of SS,[11] which falls within the multifaceted etiopathogenic spectrum of primary SS. This article analyses the current evidence on the complex relationship between HCV and SS, focusing on the specific etiopathogenic and clinical characteristics of SS diagnosed in patients with chronic HCV infection.

PREVALENCE OF HEPATITIS C VIRUS INFECTION IN SJÖGREN'S SYNDROME PATIENTS

Various studies have analyzed the prevalence of chronic HCV infection in patients with primary SS, with most finding a higher prevalence than in the general population, although the results vary according to the geographic area.[6] Studies from southern Europe describe a prevalence ranging from 10% to 20% (14% using ELISA-3 and 5%–19% using RIBA-2). In contrast, some studies from Scandinavia and the United States[12,13] have found no association between SS and HCV (prevalence <1%), possibly because of the lower prevalence of HCV infection in these countries compared with the Mediterranean area.[7] The technique of choice for screening HCV infection in patients with SS is the detection of IgG antibodies against HCV using third- or fourth-generation ELISA, because first- or second-generation ELISA may provide false-positive results. A positive result should always be confirmed by HCV-RNA detection.

Table 1
Meta-analysis of the main studies analyzing the prevalence of autoantibodies in unselected series of patients with chronic hepatitis C virus infection

Autoantibodies	Positive Markers in HCV Patients Tested (%)
Cryoglobulins	204/514 (39.7)
Rheumatoid factor	281/738 (38.1)
Anti-SMA	481/2203 (21.8)
Antinuclear antibodies	589/3169 (18.6)
Anti-LKM	75/2193 (3.4)
Anti-dsDNA	16/606 (2.6)
Anti-ENA	11/444 (2.5)
AMA	4/1210 (0.3)

Abbreviations: AMA, antimitochondrial antibodies; ENA, antiextractable nuclear antigens (anti-Ro/SS-A, anti-La/SS-B, anti-RNP, anti-Sm); HCV, hepatitis C virus; LKM, anti–liver-kidney microsomes antibodies; SMA, anti–smooth muscle antibodies.

From Ramos-Casals M, Font J. Extrahepatic manifestations in patients with chronic hepatitis C virus infection. Curr Opin Rheumatol 2005;17:447–55; with permission.

Table 2
Different degrees of association between hepatitis C virus and systemic autoimmune diseases

Degree of Association	Extrahepatic HCV Features Overlapping with the Classification Criteria
High	
Sjögren's syndrome	Xerostomia, xerophthalmia, ocular tests (+), salivary biopsy (+), ANA, RF
Rheumatoid arthritis	Arthritis of three or more joint areas, arthritis of hand joints, symmetric arthritis, RF
Systemic lupus erythematosus	Articular involvement, renal involvement, ANA, aPL, cytopenias
Intermediate	
Polyarteritis nodosa	Weakness, peripheral neuropathy, elevated creatinine, positive HBV markers
Antiphospholipid syndrome	Positive aPL, atypical thrombotic events
Sarcoidosis	Pulmonary fibrosis
Inflammatory myopathies	Weakness, elevated GOT, GPT
Low	
Systemic sclerosis	Pulmonary fibrosis
Wegener granulomatosis	Renal involvement
Giant cell arteritis	Age >50 y
Polymyalgia rheumatica	—
Ankylosing spondylitis	—

Abbreviations: ANA, antinuclear antibodies; aPL, antiphospholipid antibodies; GOT, glutamate oxalacetate transaminase; GPT, glutamic-pyruvic transaminase; HBV, hepatitis B virus; RF, rheumatoid factor.

Data from Ramos-Casals M, Jara LJ, Medina F, et al. HISPAMEC Study Group. Systemicautoimmune diseases co-existing with chronic hepatitis C virus infection (the HISPAMEC registry): patterns of clinical and immunological expression in 180 cases. J Intern Med 2005;257:549–57.

ETIOPATHOGENESIS: SIALOTROPISM AND LYMPHOTROPISM OF HEPATITIS C VIRUS

Etiopathogenically, chronic HCV infection and primary SS have different etiologies (infectious and autoimmune) but share some etiopathogenic mechanisms (**Box 1**).[10,11,14–24] Both entities are characterized by B-cell hyperactivity and are closely associated with B-cell–driven processes, such as mixed cryoglobulinemia and B-cell lymphoma. The $CD5^+$ B-cell subpopulation, a small group of B cells involved in the production of natural autoantibodies and rheumatoid factor (RF), may have a possible role in both diseases.[10]

The specific tropism of HCV for many extrahepatic cell types (**Box 2**),[23–33] especially for circulating blood cells, has recently been demonstrated by several studies[6] providing a clear link between HCV and the development of autoimmune processes. The lymphotropism of HCV links the virus to the synthesis of cryoglobulins and the development of lymphoma, whereas its sialotropism may explain the close association with sicca syndrome and SS. Recent experimental studies have found evidence supporting the sialotropism of HCV. Koike and colleagues[15] described the development of an exocrinopathy resembling SS in the salivary and lacrimal glands of transgenic mice carrying the HCV envelope genes, and suggested that the envelope proteins of HCV may recruit lymphocytes in the salivary glands leading to the formation of

Box 1
Epidemiologic, clinical, histologic, and virologic evidence for the existence of Sjögren's syndrome secondary to hepatitis C virus infection

Epidemiologic evidence

Nearly 500 reported cases of SS-HCV[11]

HCV infection in 156 (12%) of 1306 SS patients tested by ELISA[14]

Experimental evidence

Development of SS-like exocrinopathy in transgenic mice carrying the HCV envelope genes[15]

Shared clinical, histologic, and molecular characteristics in SS and HCV-related lymphomagenesis[16,17]

Histologic evidence

Positive salivary gland biopsy in 25% of HCV patients[10]

Histologically indistinguishable sialadenitis (Chisholm-Mason classification grade 3 or 4)[8,18,19]

Similar immunohistochemical characteristics of HCV-related sialadenitis[20–22]

Virologic evidence

Detection of HCV-RNA of both positive and negative polarity in epithelial cells of SS-HCV patients[23]

Detection of HCV core antigen in epithelial cells of SS-HCV patients[23]

HCV infection of salivary gland epithelial cells from SS-HCV patients[23]

Detection of HCV-RNA in salivary glands from SS-HCV patients with high HCV viremia[24]

lymphocytic infiltrates. De Vita and colleagues[34] firstly detected HCV in human salivary glands, and two additional studies[23,24] have demonstrated the capability of the HCV to infect and replicate in the salivary gland tissue of HCV patients with sicca syndrome and SS. Arrieta and colleagues[23] found that HCV infects and replicates in epithelial cells from salivary glands of patients with SS or chronic sialadenitis, a fact also confirmed by Toussirot and colleagues[24] in three SS-HCV patients. The reasons for this specific predilection of HCV for exocrine gland tissue are unknown.

CHARACTERIZATION OF SJÖGREN'S SYNDROME ASSOCIATED WITH HEPATITIS C VIRUS

Clinical studies have shown sicca symptomatology, positive ocular tests, lymphocytic infiltration of salivary glands, and autoantibodies in HCV patients,[6] and this has led to HCV infection being considered as an exclusion criterion for the diagnosis of primary SS in the most recent set of criteria, published in 2002 by the European-American Consensus study Group.[35] Patients with SS associated with chronic HCV infection have a different demographic, clinical, and immunologic profile, however, compared with patients with primary SS. Features of SS-HCV are shown in **Table 3**.

Clinical Features of Sjögren's Syndrome Hepatitis C Virus Patients

Demographically, SS-HCV is characterized by a comparatively reduced female/male ratio (4:1) and an older age at SS diagnosis.[36] Clinically, SS-HCV patients have a similar percentage of altered diagnostic tests compared with primary SS patients, with a high rate of altered ocular tests (97%), parotid scintigraphy (85%), and salivary gland biopsies (74%) (see **Table 3**). Although a similar prevalence of glandular features has been found, specific extraglandular manifestations, such as articular, vasculitic, and neuropathic involvement (the classic triad of the cryoglobulinemic syndrome), are

Box 2
Extrahepatic sites of hepatitis C virus infection

Extrahepatic tissues

Salivary glands[23,24]

Gastric mucosa[25]

Striated muscle[26,27]

Peripheral nerve[26,28]

Central nervous system[29]

Myocardium[30]

Cutaneous lesions[31]

Circulating blood cells

B lymphocytes[32,33]

T lymphocytes[32]

Monocytes[32]

Neutrophils[32]

Platelets[32]

more frequently observed in SS-HCV patients.[36] This suggests that cryoglobulinemia may play a more important role in the extraglandular features observed in SS associated with HCV than it does in primary SS. SS-HCV patients have a higher frequency of altered liver profile and also have a higher frequency of neoplasia compared with patients with primary SS.[36] The clinical expression of SS-HCV is similar to primary SS with respect to the prevalence of glandular features, altered diagnostic tests, and the percentage of fulfillment of the 2002 Criteria,[35] but shows a higher prevalence of cryoglobulinemia, liver involvement, and neoplasia.

Immunologic Profile of Sjögren's Syndrome Hepatitis C Virus

A study has found that nearly 70% of SS-HCV patients have positive ANA.[36] Two-thirds of these ANA-positive patients had negative Ro/La antibodies, an immunologic pattern (ANA positive, ENA negative) typically observed in chronic HCV infection.[6] Although negative Ro/La has been considered a typical immunologic feature of SS associated with HCV,[18,19] the authors found a subset of 68 SS-HCV patients with positive ENA, representing 25% of the SS-HCV patients studied.[36] This subset of SS-HCV-ENA–positive patients was predominantly female and had a higher prevalence of specific SS features and a lower frequency of liver involvement. This suggests that Ro/La positivity may form part of the immunologic expression of some SS-HCV patients (although at a lower level than that observed in primary SS). A higher rate of anti–Ro/La positivity has recently been reported in HCV-positive patients in whom subjective and objective sicca manifestations were more strictly selected and anti–Ro/La positivity investigated by both ELISA and immunoblot assays.[37] The alternative hypothesis, however, of a casual association between a true primary SS and HCV infection should also be considered. Immunogenetic analysis of SS-HCV-ENA–positive patients might determine whether they have similar or different genetic substrates from Ro/La–positive patients with primary SS. A recent study found a close association between HLA-DQB1*02 and sicca syndrome in patients with chronic HCV infection.[38]

Table 3
Clinical features of 483 patients with Sjögren's syndrome associated with hepatitis C virus infection

	SS-HCV Patients N = 483	%
Demographic characteristics		
Mean age at diagnosis of SS (years)	53.6	
Mean age at diagnosis of HCV (years)	55.2	
Gender F/M (ratio)	245/67 (3.65)	
Geographic area		
Southern Europe	338	70
Northern Europe	1	0.2
Central Europe	42	9.5
North America	37	8.5
Asia	50	10.4
Other countries	2	1.4
SS-related features		
Xerostomia	427/440	98
Xerophthalmia	430/440	97
Ocular tests (+)	236/242	97
Parotid scintigraphy (+)	135/159	85
Salivary gland biopsy (+)	191/259	74
ANA (+)	181/266	68
RF (+)	130/243	53
Hypocomplementemia	107/212	51
Cryoglobulinemia	147/314	47
Articular involvement	84/214	39
Anti-Ro/La (+)	68/269	25
Cutaneous vasculitis	42/214	20
Peripheral neuropathy	31/214	15
Parotidomegaly	76/214	17
Raynaud's phenomenon	27/214	13
Thyroiditis	20/214	9
Pulmonary fibrosis	12/214	6
Renal involvement	7/214	3
HCV-related features and neoplasia		
Raised transaminases	187/266	70
Neoplasia	55/331	17
Lymphoma	38/331	11
Cirrhosis	34/270	13
Hepatocellular carcinoma	9/339	3

The SS-HCV Registry, last update December 31, 2007.
Abbreviations: ANA, antinuclear antibodies; HCV, hepatitis C virus; RF, rheumatoid factor; SS, Sjögren's syndrome.

Of the reported SS-HCV patients (see **Table 3**), half presented with cryoglobulinemia, which may be considered the key immunologic marker of SS associated with HCV. Cryoglobulinemia plays an important role in the development of extraglandular features in SS-HCV. Cryoglobulins also play a predominant role in the immunologic

pattern of these patients, having a close association with hypocomplementemia and RF positivity. The RF-activity induced by HCV-related cryoglobulinemia also fulfills one of the 1993 European classification criteria for SS diagnosis. Another key immunologic marker of SS-HCV is the presence of hypocomplementemia, which is closely associated with the presence not only of circulating cryoglobulins, but also liver involvement and neoplasia.[36]

The major feature differentiating between primary and HCV-related SS is the immunologic pattern, with a predominance of cryoglobulinemic-related markers (mixed cryoglobulins, RF, hypocomplementemia) over SS-related markers (anti–Ro/SS-A and anti–La/SS-B autoantibodies) in HCV-related SS.[36] The SS-HCV Registry Study Group found a threefold higher prevalence of hypocomplementemia in SS-HCV patients compared with patients with primary SS.[39] Cryoglobulinemia seems to be the key immunologic marker of SS associated with HCV, having a close association with RF activity and complement activation.

Fulfillment of the Sjögren's Syndrome Classification Criteria

There is a considerable overlap between European diagnostic criteria for SS and some extrahepatic features of HCV infection.[39] Extrapolating from the main studies with large series of HCV patients,[6] xerostomia was observed in 158 (18%) of 859 patients; xerophthalmia in 129 (17%) of 769; positive ocular tests in 83 (38%) of 216; positive salivary gland biopsy (grades 3–4 of Chisholm-Mason classification) in 64 (25%) of 251; positive ANA in 481 (18%) of 2641; and positive RF in 357 (40%) of 1117 HCV patients. In contrast, positive anti–Ro/SS-A antibodies were described in only 30 (4%) of 765 HCV patients and anti–La/SS-B in 27 (3%) of 765 (**Table 4**).[10] These percentages suggest that a diagnosis of SS could be easily made in HCV patients presenting with sicca syndrome, positive ANA, or RF. The SS diagnosed in these HCV patients may be considered as one of the extrahepatic manifestations of chronic HCV infection.

Although some SS-HCV patients fulfilled all six European classification criteria for SS, most only fulfilled the minimum four criteria required.[36] When the criteria proposed in 2002[35] were applied in 92 SS-HCV patients in whom all diagnostic tests were performed, however, only 15% did not fulfill these more restrictive criteria, a very

Table 4
Prevalence of the 1993 European criteria for Sjögren's syndrome diagnosis in large series of patients with chronic hepatitis C virus infection

1993 European Criteria	Present Feature/HCV Patients	Prevalence %
1. Xerostomia	158/859	18
2. Xerophthalmia	129/769	17
3. Positivite ocular tests	83/216	38
4. Parotid scintigraphy	No data	No data
5. Salivary gland biopsy	64/251	25
6. Immunologic tests		
6.1. Antinuclear antibodies	481/2641	18
6.2. Rheumatoid factor	357/1117	40
6.3. Ro/SS-A	30/765	4
6.4. La/SS-B	27/765	3

From Ramos-Casals M, García-Carrasco M, Cervera R, et al. Sjögren's syndrome and hepatitis C virus. Clin Rheumatol 1999;18:93–100; with permission.

similar percentage to that observed in large series of primary SS patients.[40] The reason is the substantial number of SS-HCV patients who had one of the two mandatory 2002 criteria (positive salivary gland biopsy or anti–Ro/La antibodies). Taken together, the evidence suggests that HCV infection may account for the pathogenesis of a subgroup of patients with "primary" SS, above all patients with liver involvement or cryoglobulinemia.

DOES SJÖGREN'S SYNDROME HEPATITIS C VIRUS INCREASE THE RISK OF LYMPHOMA?

The close relationship between autoimmunity, viruses, and cancer is demonstrated by the description of patients with HCV infection, systemic autoimmune diseases, and B-cell lymphoma, who had a high prevalence of cryoglobulinemia, a high frequency of primary extranodal non-Hodgkin's lymphoma (NHL) involvement, and a poor prognosis.[41] Both SS and chronic HCV infection are characterized by an underlying B-cell hyperactivity that predisposes to monoclonal B-cell selection and, in some patients, to the development of an overt B-cell lymphoma. The association between SS and HCV infection, in addition to the possible evolution of either disease in a B-cell lymphoma, suggests that some patients may be in an additive manner;[34] however, there are few reports on a possible additive effect.[42]

B-Cell Lymphoma in Hepatitis C Virus Patients

Although lymphoma has been closely linked with primary SS in the last 30 years, the evidence of a possible association between B-cell lymphoma and HCV has been recently suggested,[16,37] although some studies have found no significant association.[17,21,43]

Recent studies have found a higher prevalence of lymphoproliferative disorders in HCV patients.[44,45] Matsuo and colleagues[46] performed an elegant meta-analysis of 23 epidemiologic studies on the association between HCV and NHL, including 4049 NHL patients. The summary odds ratio for NHL in HCV patients was 5.70, being 5.04 for B-cell and 2.51 for T-cell NHL.[46] A similar meta-analysis was conducted by Dal Maso and Franceschi.[47] This study was performed to evaluate the strength and the consistency of the association between HCV and NHL, and included only studies with greater than or equal to 100 age- and gender-adjusted cases. The pooled relative risk for all NHL in HCV-positive individuals was 2.5. Nieters and colleagues[48] tested for HCV infection in serum samples of 1807 lymphoma cases and 1788 controls, and found HCV infection in 53 (2.9%) lymphoma cases and in 41 (2.3%) control subjects (odds ratio, 1.42). When restricted to individuals who tested positive for HCV-RNA, the odds ratio increased to 1.82.

The prevalence of HCV infection in NHL patients may be higher, because Paydas and colleagues[49] have described false-negative results in the anti-HCV antibody ELISA in 8 (72%) out of 11 patients with NHL, in whom the presence of HCV-RNA was confirmed in paraffin-embedded lymphomatous tissues. This masked HCV infection has also been described in some patients with an altered liver profile of unknown origin,[50] in whom the virus was isolated from liver tissue and circulating mononuclear cells, and was not detectable by ELISA and polymerase chain reaction techniques in serum.

Lymphomagenesis in Hepatitis C Virus and Sjögren's Syndrome Patients

Lymphomagenesis in HCV patients might be initiated by the chronic stimulation of polyclonal B cells by the virus[51] and the compartmentalization of HCV quasispecies in blood mononuclear cells,[52] with the subsequent development of specific B-cell clonal expansions[53,54] and procarcinogenic mutations.[55,56] Vallat and colleagues[54]

suggested that B-cell clonality in the blood and liver may be a marker of lymphoma development in some HCV patients. Machida and colleagues[55] reported that both acute and chronic HCV infection caused a 5- to 10-fold increase in mutation frequency in the Ig heavy chain, bcl-6, p53, and beta-catenin genes. Libra and colleagues[56] detected bcl-2 rearrangement in mucosa-associated lymphoid tissue (MALT) lymphomas from HCV patients. Rosa and colleagues[57] have recently proposed that CD81-mediated activation of B cells in vitro mimics the effects of HCV binding to B cell CD81 in vivo and that polyclonal proliferation of naive B lymphocytes is a key initiating factor for the development of HCV-associated B-lymphocyte disorders.

The sialotropism and lymphotropism of HCV suggests the probability of the development of both SS and lymphoproliferative processes in some patients with chronic HCV infection, and recent studies have reported similarities in the etiopathogenic mechanisms of lymphoma development in both SS and HCV patients.[16,17] Ambrosetti and colleagues[58] have reported that most cases of primary salivary MALT lymphoma are associated either with SS or HCV infection. In addition, Arcaini and colleagues[59] retrospectively studied 172 patients with a histologic diagnosis of marginal zone B-cell MALT lymphoma, in whom HCV infection was found in 60 patients (35%). HCV-positive patients showed more frequent skin (35%), salivary glands (25%), and orbit (15%) lymphomatous involvement. In addition, De Re and colleagues[16] described remarkable homologies between the antigen combinatory regions of the IgR expressed by both SS- and HCV-associated lymphoproliferative diseases, which suggest an immunologic cross-reactivity or molecular mimicry among the agents that underlie these disorders.

Characterization of B-Cell Lymphoma in Sjögren's Syndrome Hepatitis C Virus Patients

A recent study[60] has firstly described the disease characteristics of B-cell lymphoma in SS-HCV patients, its treatment, outcome, and survival prognosis. Compared with SS-HCV patients without lymphoma, those with lymphoma had a higher frequency of parotid enlargement and vasculitis.[60] In primary SS, parotid enlargement is considered as a highly suggestive clinical sign of lymphoma,[3,61] whereas vasculitic features are closely associated with cryoglobulinemia[62] and lymphoma,[61,63] with cryoglobulins being shown to be predictive factors for lymphoma development.[64] This suggests a close association between cryoglobulinemic syndrome and lymphoma in SS-HCV patients, either in its asymptomatic (circulating cryoglobulins) or symptomatic (cryoglobulinemic vasculitis) form.

Immunologically, nearly all SS-HCV patients who developed B-cell lymphoma had RF posivity.[60] The secretion of RF by polyclonally activated B cells has been related to lymphoma development in both SS and HCV infection, but not to other RF-positive diseases, such as rheumatoid arthritis.[65] In primary SS, lymphoma seems to be triggered by RF-secreting B cells closely associated with the 17,109 and G-6 Ig idiotypes,[64] whereas in HCV patients, a possible association with an antibody response to the envelope protein E2 of the virus has been postulated.[51] The coexistence of both RF-positive processes (SS and HCV) in the same patient might enhance the possibility of developing diseases related to B-cell proliferation (cryoglobulinemia and low- and high-grade lymphoma).[66] Although RF has not been described as a predictive factor for lymphoma in primary SS or HCV, it should be considered a novel predictive factor for lymphoma development in SS-HCV patients.

The most frequent type of B-cell lymphoma found in SS-HCV patients is MALT lymphoma, in contrast to unselected HCV patients, in whom high-grade lymphoma is the most frequent.[60] The predominance of MALT lymphoma in SS-HCV and primary SS but not in HCV suggests an important role for SS in the lymphomagenesis

of patients with SS-HCV. Recent studies have also demonstrated a predominance of low-grade lymphoma in HCV patients with other associated autoimmune diseases, such as cryoglobulinemia.[67,68] In addition, SS-HCV patients show a predominant extranodal location of B-cell lymphoma in the exocrine glands, liver, and stomach.[60] HCV can infect and replicate in these organs leading to in situ polyclonal B-cell activation and RF production. This may lead to these organs becoming the initial sites of B-cell neoplastic transformation.[60] The predominant involvement of the parotid gland in both SS-HCV patients and patients with primary SS[61] reinforces the etiopathogenic similarity between SS-HCV lymphoma and SS-related lymphoma compared with HCV-related lymphoma.

Treatment of B-Cell Lymphoma in Sjögren's Syndrome Hepatitis C Virus Patients

The treatment of B-cell lymphoma in SS-HCV patients is a clinical challenge because of the confluence of various specific characteristics, including the age of the patients, other drug treatments, the concomitant autoimmune features, and the HCV-related liver disease. Unfortunately, no data are available for the therapeutic management of lymphoma in SS-HCV patients. In B-cell lymphomas, diverse therapeutic options have been used including conventional chemotherapy,[61] monoclonal agents,[69] antiviral[70] or antimicrobial[71] agents, and in some cases no specific therapy.[12] In SS-HCV patients two therapeutic options should be highlighted as future options. The first is the use of monoclonal agents against B cells (rituximab), which have been successfully used to treat not only B-cell lymphomas[72] but also cryoglobulinemic vasculitis,[73] with the aim of controlling the marked B-cell hyperreactivity observed in SS-HCV patients. The second is the use of antiviral agents (interferon and ribavirin), which aims to eradicate the virus as the main causative agent of this B-cell hyperactivity, and which was successfully used in some of the authors' cases. Tursi and colleagues[74] have recently demonstrated the disappearance of gastric MALT lymphoma in 13 out of 18 HCV patients after 6 months of antiviral therapy. In addition, recent studies have described an association between splenic lymphoma with villous lymphocytes and HCV.[75–77] A combination of rituximab and antiviral therapy may be a promising option for the successful treatment of B-cell lymphomas in patients with SS-HCV.

The additive association between SS and HCV in the pathogenesis of B-cell lymphoma suggests an important role for the association of autoimmune and chronic viral diseases in the pathogenesis of B-cell lymphoproliferative disorders and reinforces the idea that autoimmunity, infection, and cancer may be closely related. A careful evaluation and follow-up of HCV patients with associated SS to aid early diagnosis and treatment of possible B-cell lymphoma should be recommended.

SUMMARY

This article describes the broad clinical expression of SS associated with HCV, which includes both hepatic and extrahepatic features, specific immunologic abnormalities, and neoplastic processes (**Fig. 1**). As in primary SS, various clinical and immunologic subsets may be identified, which define more homogeneous patterns of clinical expression. The clinical expression of SS-HCV is similar to primary SS with respect to the prevalence of glandular features and the percentage of fulfillment of the 2002 Criteria, but shows a higher prevalence of cryoglobulinemia, liver involvement, and neoplasia. The immunologic expression of SS-HCV includes a greater presence of ANA positive, ENA negative (because of the lower frequency of anti–Ro/La antibodies) and cryoglobulinemia (which also explains the higher prevalence of RF positivity and

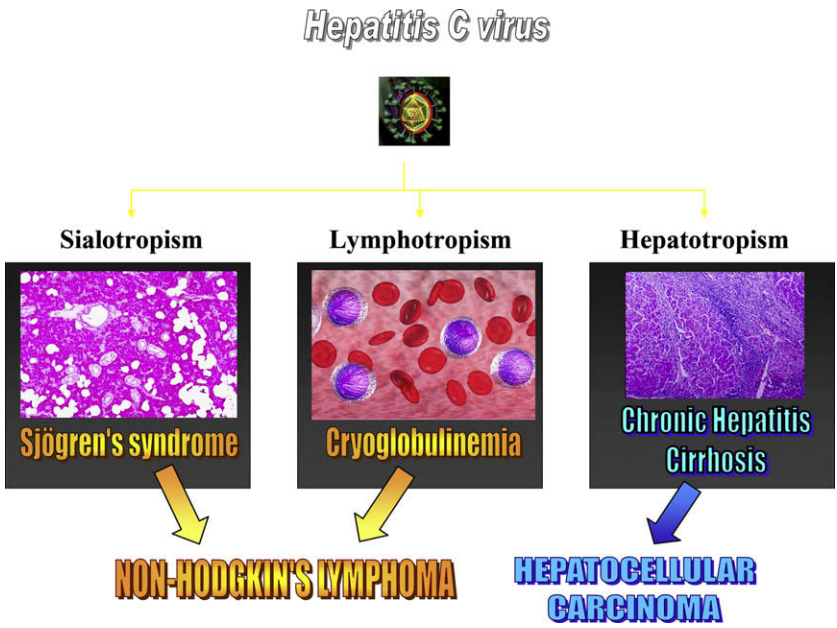

Fig. 1. Close association between HCV, SS, cryoglobulinemia, and B-cell lymphoproliferative diseases.

low complement levels). The 10 epidemiologic, clinical, and immunologic criteria that should alert clinicians to the possible existence of an underlying chronic HCV infection in a patient with primary SS are as follows:

Epidemiologic characteristics
1. Male gender
2. Older age at SS diagnosis

Clinical features
3. Cutaneous vasculitis
4. Peripheral neuropathy
5. Liver involvement (clinical or analytic)
6. Neoplasia (lymphoma or hepatocellular carcinoma)

Immunologic parameters
7. Cryoglobulins
8. Rheumatoid factor
9. Hypocomplementemia
10. Negative Ro/La

In patients with SS associated with HCV, the term "SS secondary to HCV" should be used in patients who fulfill the 2002 Classification Criteria and the term "sicca syndrome secondary to HCV" should be used in those who fulfill only three criteria or who only fulfill the 1993 European Criteria. Chronic HCV infection should be considered an exclusion criterion for the classification of primary SS, not because it mimics primary SS, but because the virus may be implicated in the development of SS in a specific subset of patients.

REFERENCES

1. Ramos-Casals M, Tzioufas AG, Font J. Primary Sjögren's syndrome: new clinical and therapeutic concepts. Ann Rheum Dis 2005;64:347–54.
2. Ramos-Casals M, Font J. Primary Sjögren's syndrome: current and emergent etiopathogenic concepts. Rheumatology (Oxford) 2005;44:1354–67.
3. Fox RI. Sjogren's syndrome. Lancet 2005;366:321–31.
4. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjogren syndrome. Arch Intern Med 2004;164:1275–84.
5. Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989;244:359–62.
6. Ramos-Casals M, Font J. Extrahepatic manifestations in patients with chronic hepatitis C virus infection. Curr Opin Rheumatol 2005;17:447–55.
7. Ramos-Casals M, Jara LJ, Medina F, et al. HISPAMEC Study Group. Systemic autoimmune diseases co-existing with chronic hepatitis C virus infection (the HISPAMEC registry): patterns of clinical and immunological expression in 180 cases. J Intern Med 2005;257:549–57.
8. Haddad J, Deny P, Munz-Gotheil C, et al. Lymphocytic sialadenitis of Sjögren's syndrome associated with chronic hepatitis C virus liver disease. Lancet 1992;339:321–3.
9. Ramos-Casals M, Brito-Zerón P, Font J. Lessons from diseases mimicking Sjögren's syndrome. Clin Rev Allergy Immunol 2007;32:275–83.
10. Ramos-Casals M, García-Carrasco M, Cervera R, et al. Sjögren's syndrome and hepatitis C virus. Clin Rheumatol 1999;18:93–100.
11. Ramos-Casals M, García-Carrasco M, Zeron MP, et al. Viral etiopathogenesis of Sjögren's syndrome: role of the hepatitis C virus. Autoimmun Rev 2002;1: 238–43.
12. Verbaan H, Carlson J, Eriksson S, et al. Extrahepatic manifestations of chronic hepatitis C infection and the interrelationship between primary Sjögren's syndrome and hepatitis C in Swedish patients. J Intern Med 1999;245: 127–32.
13. King PD, McMurray RW, Becherer PR. Sjögren's syndrome without mixed cryoglobulinemia is not associated with hepatitis C virus infection. Am J Gastroenterol 1994;89:1047–50.
14. Garcia-Carrasco M, Font Franco J, Ingelmo Morin M, et al. [Clinical manifestations and immunology associated with chronic infection with hepatitis C virus]. Rev Clin Esp 2002;202:224–32 [in Spanish].
15. Koike K, Moriya K, Ishibashi K, et al. Sialadenitis histologically resembling Sjögren syndrome in mice transgenic for hepatitis C virus envelope genes. Proc Natl Acad Sci U S A 1997;94:233–6.
16. De Re V, De Vita S, Gasparotto D, et al. Salivary gland B cell lymphoproliferative disorders in Sjögren's syndrome present a restricted use of antigen receptor gene segments similar to those used by hepatitis C virus–associated non Hodgkin's lymphomas. Eur J Immunol 2002;32:903–10.
17. Mariette X. Lymphomas complicating Sjögren's syndrome and hepatitis C virus infection may share a common pathogenesis: chronic stimulation of rheumatoid factor B cells. Ann Rheum Dis 2001;60:1007–10.
18. Jorgensen C, Legouffe MC, Perney P, et al. Sicca syndrome associated with hepatitis C virus infection. Arthritis Rheum 1996;39:1166–71.
19. Ramos-Casals M, Garcia-Carrasco M, Cervera R, et al. Hepatitis C virus infection mimicking primary Sjogren syndrome: a clinical and immunologic description of 35 cases. Medicine (Baltimore) 2001;80:1–8.

20. Coll J, Gambus G, Corominas J, et al. Immunochemistry of minor salivary gland biopsy specimens from patients with Sjögren's syndrome with and without hepatitis C virus. Ann Rheum Dis 1997;56:390–2.
21. Pawlotsky JM, Ben Yahia M, Andre C, et al. Immunological disorders in C virus chronic active hepatitis: a prospective case-control study. Hepatology 1994;19:841–8.
22. Scott CA, Avellini C, Desinan L, et al. Chronic lymphocytic sialoadenitis in HCV-related chronic liver disease: comparison of Sjögren's syndrome. Histopathology 1997;30:41–8.
23. Arrieta JJ, Rodriguez-Inigo E, Ortiz-Movilla N, et al. In situ detection of hepatitis C virus RNA in salivary glands. Am J Pathol 2001;158:259–64.
24. Toussirot E, Le Huede G, Mougin C, et al. Presence of hepatitis C virus RNA in the salivary glands of patients with Sjogren's syndrome and hepatitis C virus infection. J Rheumatol 2002;29:2382–5.
25. De Vita S, De Re V, Sansonno D, et al. Gastric mucosa as an additional extrahepatic localization of hepatitis C virus: viral detection in gastric low-grade lymphoma associated with autoimmune disease and in chronic gastritis. Hepatology 2000;31:182–9.
26. Authier FJ, Bassez G, Payan C, et al. Detection of genomic viral RNA in nerve and muscle of patients with HCV neuropathy. Neurology 2003;60:808–12.
27. Di Muzio A, Bonetti B, Capasso M, et al. Hepatitis C virus infection and myositis: a virus localization study. Neuromuscul Disord 2003;13:68–71.
28. Bonetti B, Scardoni M, Monaco S, et al. Hepatitis C virus infection of peripheral nerves in type II cryoglobulinemia. Virchows Arch 1999;434:533–5.
29. Radkowski M, Wilkinson J, Nowicki M, et al. Search for hepatitis C virus negative-strand RNA sequences and analysis of viral sequences in the central nervous system: evidence of replication. J Virol 2002;76:600–8.
30. Okabe M, Fukuda K, Arakawa K, et al. Chronic variant of myocarditis associated with hepatitis C virus infection. Circulation 1997;96:22–4.
31. Agnello V, Abel G. Localization of hepatitis C virus in cutaneous vasculitic lesions in patients with type II cryoglobulinemia. Arthritis Rheum 1997;40:2007–15.
32. Crovatto M, Pozzato G, Zorat F, et al. Peripheral blood neutrophils from hepatitis C virus-infected patients are replication sites of the virus. Haematologica 2000; 85:356–61.
33. Ducoulombier D, Roque-Afonso AM, Di Liberto G, et al. Frequent compartmentalization of hepatitis C virus variants in circulating B cells and monocytes. Hepatology 2004;39:817–25.
34. De Vita S, Sansonno D, Dolcetti R, et al. Hepatitis C virus infection within a malignant lymphoma lesion in the course of type II mixed cryoglobulinemia. Blood 1995;86:1887–92.
35. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
36. Ramos-Casals M, Loustaud-Ratti V, De Vita S, et al. SS-HCV Study Group. Sjogren syndrome associated with hepatitis C virus: a multicenter analysis of 137 cases. Medicine (Baltimore) 2005;84:81–9.
37. De Vita S, Damato R, De Marchi G, et al. True primary Sjögren's syndrome in a subset of patients with hepatitis C infection: a model linking chronic infection to chronic sialadenitis. Isr Med Assoc J 2002;4:1101–5.
38. Smyth CM, McKiernan SM, Hagan R, et al. Chronic hepatitis C infection and sicca syndrome: a clear association with HLA DQB1*02. Eur J Gastroenterol Hepatol 2007;19:493–8.

39. Ramos-Casals M, Theander E, Tzioufas AG, et al. Digestive involvement in primary Sjögren syndrome. In: Font J, Ramos-Casals M, Rodés J, et al, editors. Digestive involvement of autoimmune diseases. Amsterdam: Elsevier; 2008. p. 71–81 .
40. Garcia-Carrasco M, Ramos-Casals M, Rosas J, et al. Primary Sjogren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 2002;81:270–80.
41. Ramos-Casals M, Trejo O, Garcia-Carrasco M, et al. Triple association between hepatitis C virus infection, systemic autoimmune diseases, and B cell lymphoma. J Rheumatol 2004;31:495–9.
42. De Vita S, Zagonel V, Russo A, et al. Hepatitis C virus, non-Hodgkin's lymphomas and hepatocellular carcinoma. Br J Cancer 1998;77:2032–5.
43. Ramos-Casals M, Font J, Garcia-Carrasco M, et al. Primary Sjogren syndrome: hematologic patterns of disease expression. Medicine (Baltimore) 2002;81:281–92.
44. Bianco E, Marcucci F, Mele A, et al. Italian multi-center case-control study. Prevalence of hepatitis C virus infection in lymphoproliferative diseases other than B-cell non-Hodgkin's lymphoma, and in myeloproliferative diseases: an Italian multi-center case-control study. Haematologica 2004;89:70–6.
45. Morton LM, Engels EA, Holford TR, et al. Hepatitis C virus and risk of non-Hodgkin lymphoma: a population-based case-control study among Connecticut women. Cancer Epidemiol Biomarkers Prev 2004;13:425–30.
46. Matsuo K, Kusano A, Sugumar A, et al. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. Cancer Sci 2004;95:745–52.
47. Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev 2006;15:2078–85.
48. Nieters A, Kallinowski B, Brennan P, et al. Hepatitis C and risk of lymphoma: results of the European multicenter case-control study EPILYMPH. Gastroenterology 2006;131:1879–86.
49. Paydas S, Ergin M, Tanriverdi K, et al. Detection of hepatitis C virus RNA in paraffin-embedded tissues from patients with non-Hodgkin's lymphoma. Am J Hematol 2004;76:252–7.
50. Castillo I, Pardo M, Bartolome J, et al. Occult hepatitis C virus infection in patients in whom the etiology of persistently abnormal results of liver-function tests is unknown. J Infect Dis 2004;189:7–14.
51. Starkebaum G, Sasso EH. Hepatitis C and B cells: induction of autoimmunity and lymphoproliferation may reflect chronic stimulation through cell-surface receptors. J Rheumatol 2004;31:416–8.
52. Di Liberto G, Roque-Afonso AM, Kara R, et al. Clinical and therapeutic implications of hepatitis C virus compartmentalization. Gastroenterology 2006;131(1): 76–84.
53. Sansonno D, Lauletta G, De Re V, et al. Intrahepatic B cell clonal expansions and extrahepatic manifestations of chronic HCV infection. Eur J Immunol 2004;34:126–36.
54. Vallat L, Benhamou Y, Gutierrez M, et al. Clonal B cell populations in the blood and liver of patients with chronic hepatitis C virus infection. Arthritis Rheum 2004;50:3668–78.
55. Machida K, Cheng KT, Sung VM, et al. Hepatitis C virus induces a mutator phenotype: enhanced mutations of immunoglobulin and protooncogenes. Proc Natl Acad Sci U S A 2004;101:4262–7.

56. Libra M, De Re V, Gloghini A, et al. Detection of bcl-2 rearrangement in mucosa-associated lymphoid tissue lymphomas from patients with hepatitis C virus infection. Haematologica 2004;89:873–4.
57. Rosa D, Saletti G, De Gregorio E, et al. Activation of naive B lymphocytes via CD81, a pathogenetic mechanism for hepatitis C virus-associated B lymphocyte disorders. Proc Natl Acad Sci U S A 2005;102:18544–9.
58. Ambrosetti A, Zanotti R, Pattaro C, et al. Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with Sjogren syndrome or hepatitis C virus infection. Br J Haematol 2004;126:43–9.
59. Arcaini L, Burcheri S, Rossi A, et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. Ann Oncol 2007;18:346–50.
60. Ramos-Casals M, la Civita L, de Vita S, et al. Characterization of B cell lymphoma in patients with Sjögren's syndrome and hepatitis C virus infection. Arthritis Rheum 2007;57:161–70.
61. Voulgarelis M, Dafni UG, Isenberg DA, et al. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome. Arthritis Rheum 1999;42:1765–72.
62. Ramos-Casals M, Cervera R, Yague J, et al. Cryoglobulinemia in primary Sjögren's syndrome: prevalence and clinical characteristics in a series of 115 patients. Semin Arthritis Rheum 1998;28:200–5.
63. Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjögren's syndrome: a prospective cohort study. Arthritis Rheum 2004; 50:1262–9.
64. Tzioufas AG, Boumba DS, Skopouli FN, et al. Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjögren's syndrome. Arthritis Rheum 1996;39:767–72.
65. Dorner T, Egerer K, Feist E, et al. Rheumatoid factor revisited. Curr Opin Rheumatol 2004;16:246–53.
66. Mazzaro C, Tirelli U, Pozzato G. Hepatitis C virus and non-Hodgkin's lymphoma 10 years later. Dig Liver Dis 2005;37:219–26.
67. Monti G, Pioltelli P, Saccardo F, et al. Incidence and characteristics of non-Hodgkin lymphomas in a multicenter case file of patients with hepatitis C virus-related symptomatic mixed cryoglobulinemias. Arch Intern Med 2005;165: 101–5.
68. Dammacco F, Sansonno D, Piccoli C, et al. The cryoglobulins: an overview. Eur J Clin Invest. 2001;31:628–38.
69. Gottenberg JE, Guillevin L, Lambotte O, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005;64:913–20.
70. Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. J Clin Oncol 2005;23:468–73.
71. Salam I, Durai D, Murphy JK, et al. Regression of primary high-grade gastric B-cell lymphoma following *Helicobacter pylori* eradication. Eur J Gastroenterol Hepatol 2001;13:1375–8.
72. Furman RR, Coleman M, Leonard JP. Epratuzumab in non-Hodgkin's lymphomas. Curr Treat Options Oncol 2004;5:283–8.
73. Zaja F, De Vita S, Mazzaro C, et al. Efficacy and safety of rituximab in type II mixed cryoglobulinemia. Blood 2003;101:3827–34.

74. Tursi A, Brandimarte G, Torello M. Disappearance of gastric mucosa-associated lymphoid tissue in hepatitis C virus-positive patients after anti-hepatitis C virus therapy. J Clin Gastroenterol 2004;38:360–3.
75. Saadoun D, Suarez F, Lefrere F, et al. Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity? Blood 2005;105:74–6.
76. Kelaidi C, Rollot F, Park S, et al. Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphomas. Leukemia 2004;18:1711–6.
77. Iannitto E, Ambrosetti A, Ammatuna E, et al. Splenic marginal zone lymphoma with or without villous lymphocytes: hematologic findings and outcomes in a series of 57 patients. Cancer 2004;101:2050–7.

Involvement of Nervous System Pathways in Primary Sjögren's Syndrome

Barbara Segal, MD[a,*], Adam Carpenter, MD[b], David Walk, MD[b]

KEYWORDS

• Sjögren's syndrome • Neurologic disorders

Sjögren's syndrome (SS) is a chronic systemic autoimmune disease characterized by inflammation and dysfunction of the exocrine glands. The prevalence of primary Sjögren's syndrome (pSS) is estimated to be approximately 0.6% (95% confidence interval, 0.19%–1.39%), with a ninefold greater incidence in women compared with men. Between 1 and 4 million people in the United States are affected.[1] Secondary SS, in which patients have a pre-existing connective tissue disorder, typically systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or systemic sclerosis, accounts for approximately one-half of the cases.[2]

Diagnosis of SS is delayed on average until between 6 and 10 years after the onset of symptoms, possibly as a result of the nonspecific nature of presenting features.[3,4] While the cardinal manifestations of ocular and oral dryness are the initial symptoms in 45% to 50% of patients with pSS, fatigue and joint and muscle pain are also common early symptoms. Furthermore, in a minority of pSS patients, the initial symptoms are neurologic.[5–8] Onset of a neurologic disorder can precede the diagnosis of pSS in 40% to 80% of cases of neurologic involvement.[4,5,7–9] Overall, 65% of pSS patients will experience extra-glandular features of Sjögren's syndrome, including pulmonary, hematologic, gastrointestinal, and neurologic disorders.[10]

The spectrum of neurologic disorders associated with pSS is broad. Neurologic complications range from symptomatic brain lesions, meningitis, myelopathy, cranial neuronopathy, sensorimotor polyneuropathy, and mononeuritis multiplex, all of which are well-recognized manifestations of several systemic connective tissue disorders, to the syndrome of pure sensory neuropathy, which is relatively unique to pSS among

[a] Division of Rheumatic and Autoimmune Disorders, University of Minnesota Medical School, MMC 108, 420 Delaware SE, Minneapolis, MN 55455, USA
[b] Department of Neurology, University of Minnesota Medical School, 516 Delaware Street SE, Minneapolis, MN 55455, USA
* Corresponding author.
E-mail address: segal017@umn.edu (B. Segal).

Rheum Dis Clin N Am 34 (2008) 885–906
doi:10.1016/j.rdc.2008.08.001 rheumatic.theclinics.com
0889-857X/08/$ – see front matter

patients with connective tissue disease. Patients with an overlap syndrome who meet criteria for both pSS and SLE may be the subgroup with the highest prevalence of neurologic involvement.[11] Diagnosis of pSS according to the current American European Consensus Group (AECG) criteria requires that at least four of the following six items be present: subjective xerophthalmia, subjective xerostomia, objective tests of xerophthalmia, objective evidence of salivary gland dysfunction, presence of either anti-Ro/SSA or anti-La/SSB antibodies, and histopathologic criteria for pSS on minor salivary gland biopsy. One of the four criteria must be either positive serology or positive histopathology, with focus score equal to 1 or greater.[12] In patients who present with extra-glandular involvement without sicca symptoms, a diagnosis of pSS is possible if both a positive serologic test is found and histologic criteria for pSS are met.

Since the adoption of the international consensus criteria in 2002, the prevalence and clinical profile of Sjögren's syndrome has been shown to be similar in multiple populations.[13–16] While progress has been made in elucidating the pathogenesis of the autoimmune exocrinopathy of pSS, the pathologic mechanisms mediating neurologic disorders in pSS are not well understood. Selection of appropriate therapy for the patient with SS and neurologic involvement is challenging, given the prevailing paucity of evidence regarding the prognosis and response to treatment of many of the neurologic manifestations of pSS. This article describes the clinical syndromes of nervous system involvement found in SS, discusses the putative mechanisms of neuronal damage, and summarizes the diagnostic and current therapeutic approaches.

CLASSIFICATION OF NERVOUS SYSTEM INVOLVEMENT

Neuropsychologic Features

Multiple neuropsychologic domains are affected by pSS, including cognition, mood, and sleep.[17–23] Valdotysdottir and colleagues[24,25] reported that psychiatric diagnoses (anxiety and depression) are more prevalent among patients with pSS than age- and gender-matched controls or patients with RA. Fatigue, pain, and depression play a significant role in poor overall health status in SS patients.[13,26] Multiple studies of pSS have found a prevalence of depression in approximately 30%.[9,27–29] Additionally, a high prevalence of personality disorders, particularly somatization and hypochondriasis, has also been reported in three studies.[22,29,30] Although higher scores on the hypochondriasis and hysteria scales of the Minnesota Multiphasic Personality Inventory are described, it remains unclear whether the apparent somatization that appears to be prevalent among pSS patients reflects pre-existing personality disorder, adjustment to chronic illness, or possibly misclassification of the sicca, musculoskeletal, and neuropsychiatric features attributable primarily to Sjögren's syndrome.

The primacy of the role played by depression and somatization in the maintenance of fatigue in pSS and other autoimmune diseases is an area of controversy. Data from a recent prospective study of a community-based cohort of pSS found that, whereas abnormal fatigue was reported by 67% of pSS patients, the majority of patients who reported abnormal fatigue were not depressed, suggesting that depression is not the primary cause of pSS fatigue.[31] In pSS, as well as in SLE, psychiatric diagnosis and fatigue have been correlated with a history of neurologic disorders, suggesting a possible organic basis for affective disorders and fatigue.[22,32]

Estimates of the prevalence of central nervous system (CNS) disorders in pSS vary widely from 2.5% to 60%, reflecting lack of consensus regarding the criteria for patient selection.[4,5,9,33,34] Controversy exists, particularly over the inclusion of patients with minor cognitive disturbance and depression. Difficulties with attention, concentration, memory, and new learning are commonly reported problems; however, the specificity

of these findings is questionable, as it is estimated that as many as 50% of healthy individuals report memory problems.[35,36] Furthermore, persons with depression commonly overestimate the degree of cognitive dysfunction they are experiencing.[37] Subcortical patterns of cognitive impairment have been reported in small series; however, case-controlled studies of cognitive status comparing pSS subjects to healthy controls are scarce.[27,38,39] A similar pattern of subcortical cognitive impairment has been reported in late-life depression in persons who do not have pSS.[20,22]

Pain, sleep disturbance, and depression may all contribute to the pathogenesis of abnormal cognitive function in patients with SS. Studies of the cognitive features of primary SS to date have been limited in size or highly selected.[20,22,28,38,39] Lafitte and colleagues[5] reported on 36 patients with pSS who were referred to internal medicine or to neurology clinics at a single institution. Cognitive dysfunction was documented in 8 out of 36 (22%) and was not associated with depression. Brain MRI was normal or showed only nonspecific areas of high-signal intensity on T2-weighted images in the periventricular white matter. In the two subjects who had intellectual decline and evidence of cortical involvement, in addition to subcortical dysfunction, there were overt signs of focal CNS involvement (tetrapyramidal and pseudobulbar syndrome in both and cerebellar syndrome in one). Cases of severe cognitive dysfunction or dementia attributed to CNS involvement are rare in pSS; however, recurrent meningoencephalitis and chronic encephalopathy have been reported, as well as a steroid-responsive dementia.[40] Larger, controlled studies with sufficient statistical power are needed to define whether a specific pattern of cognitive impairment is associated with pSS and to clarify the relationship between cognitive dysfunction and depression.

Focal Central Nervous System Disorders

The clinical profile of CNS abnormalities described in association with pSS is similar to that reported in CNS lupus, and includes optic neuropathy, hemiparesis, movement disorders, brainstem and cerebellar syndromes, recurrent transient ischemic attacks, and motor neuron syndrome. Differentiation between SLE and pSS with CNS involvement can be particularly difficult, as focal neurologic deficits, oligoclonal bands in the cerebral spinal fluid (CSF), and abnormalities on MRI are detected in both SLE and SS patients.[4,5,34] The prevalence of serious focal and multifocal CNS involvement is low, in the range of 2% to 10% in multiple studies, particularly in those studies that assessed the frequency of CNS disorders among patients referred to rheumatology clinics.[5,9,20,22,27,33,34]

Spinal cord syndromes reported in pSS include transverse myelitis and progressive myelopathy, resembling primary progressive multiple sclerosis.[4,5,41] Both isolated optic neuritis and myelopathy have been described in pSS patients who are seronegative.[42] Case reports of pSS presenting with isolated optic neuropathy suggest consideration of pSS in the differential diagnosis of optic neuropathy.[43,44] Neuromyelitis optica (NMO, also known as Devic's syndrome) is an inflammatory neurologic disease characterized by recurrent episodes of myelitis and optic neuritis. NMO has been reported in association both with SLE and with pSS (**Fig. 1**), but it is unclear whether the association is beyond that expected by chance. A recent report described two cases of pSS among 153 consecutive patients with confirmed or suspected NMO, a prevalence (1.3%) marginally higher than that of pSS in the general population.[45] However, the cases of pSS were identified by prior diagnosis rather than prospective evaluation for SS, thus the co-occurrence of pSS and NMO may be higher than suggested by this study.

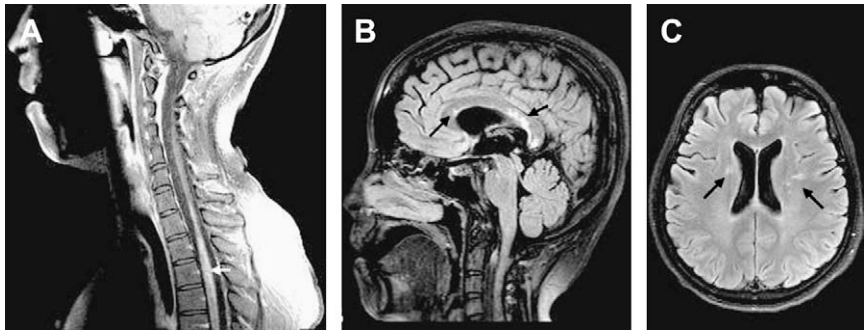

Fig. 1. MRI of a 23-year-old woman with pSS and neuromyelitis optica. The patient has a history of bilateral optic neuropathy and has had recurrent episodes of myelitis since age 11. (*A*) Cervical spine MRI shows a gadolinium-enhancing cord lesion extending from C7-T4 (*white arrow*). Brain MRI shows T2-hyperintense lesions in the corpus callosum (*B*) and in the subcortical and periventricular white matter (*C*) (*black arrows*).

Primary Sjögren's syndrome can mimic or coexist with multiple sclerosis (MS),[42,46,47] thereby presenting significant diagnostic and therapeutic dilemmas. Alexander and colleagues[46] reported an unusual series of 20 pSS patients with multifocal neurologic disease in whom the clinical features, evoked potentials, and CSF fluid profiles met criteria for definite MS, although a high proportion of these patients had features of systemic disease (cutaneous vasculitis, peripheral neuropathy, and myositis) not found in MS patients. De Seze and colleagues[48] studied 60 consecutive patients with the relatively rare primary progressive form of MS, 10 of whom (17%) met criteria for pSS. Other studies of MS populations have not found unequivocally higher prevalence of pSS than that expected in the general population.[49–51]

A much stronger association between pSS and MS was reported by Wang and colleagues,[47] who found that 6 of 12 consecutive Taiwanese patients with relapsing-remitting MS also met AECG criteria for pSS. However, many if not most of these patients appear to have had the optic-spinal variant of MS, which is particularly frequent in the Asian population and thought to represent NMO rather than MS.[52,53] Ultimately, a statistical association between pSS and MS or NMO remains suspected but unproven.

Peripheral Nervous System Involvement

As is the case with CNS involvement, neuropathy can be the presenting feature of pSS.[4,9,54,55] Neuropathic symptoms preceded sicca symptoms in about 40% of the patients described by Mellgren and colleagues.[7] Grant and colleagues[56] described patients with neuropathy and mild sicca who did not develop other extra-glandular manifestations of pSS over long-term follow-up, despite evidence of pSS on minor salivary gland biopsy. Classification of such patients is difficult, as the evolution of pSS has been observed as long as 12 years following presentation with neuropathy.[57]

Sensory neuronopathy, in which the primary pathology is in the cell body in the dorsal root or trigeminal ganglion rather than the axon, is considered distinctive of pSS. In addition, sensorimotor neuropathies, sensory neuropathies, cranial neuropathies, autonomic neuropathy, and mononeuropathy multiplex have been reported.[4,5,7,9,57–59] While sensory and sensorimotor neuropathies are the most frequently reported type of peripheral nervous system involvement, there are also case reports of acute (Guillain Barré syndrome)[60] and chronic demyelinating polyneuropathy.[5]

Differences in the profile of peripheral nervous system involvement in various studies are attributable to differences in patient selection criteria and diagnostic approaches. For example, in a recent population-based study, the predominant abnormality was prolongation of F-wave latencies interpreted as evidence of subclinical demyelinating motor neuropathy. Small fiber sensory neuropathy was rare in this cohort.[61] By contrast, series originating in neurology clinics[57] indicate that sensory predominant neuropathy or sensory neuronopathy are the most common presentation among patients with pSS and peripheral nervous system disease.

In pSS patients with peripheral nervous system involvement, the predominant clinical manifestation may depend on whether the dorsal root sensory ganglion is the primary target or the perivascular endoneurial wall. Evolution over time of small fiber neuropathy developing into a sensory ataxic neuronopathy has been reported and suggests that, at least in some pSS patients, inflammation within the dorsal root ganglion initially affects the neurons that convey small fiber modalities.[57] Clinical pathologic correlation has suggested that in the majority of cases, sensory ataxia, painful sensory neuropathies, and trigeminal neuropathy are related to a sensory ganglionitis, whereas mononeuritis multiplex and multiple cranial neuropathies are more closely associated with a peripheral nerve vasculitis.[54,57,62,63] In 558 consecutive pSS patients evaluated by Ramos-Casals and colleagues,[10] peripheral neuropathy was strongly associated with the presence of cutaneous vasculitis (31% versus 4%, $P<.001$).

Dysfunction of small-caliber neurons may be far more common than suggested by previous studies. Burning pain, pain on light stroking of the skin, attacks of pain without seeming provocation, and subtle sensory deficits are features of a neuropathic process that may be under-recognized in patients with SS. In a recent large survey of pSS patients, 70% reported symptoms suggestive of neuropathic pain. Symptoms were significantly more often reported by pSS patients than age- or gender-matched controls after controlling for fibromyalgia and depression, suggesting that subclinical painful sensory neuronopathy or neuropathy may be quite frequent.[64]

PUTATIVE MECHANISMS OF NEURONAL DAMAGE

Vasculopathy

Histopathologic descriptions of nervous system disorders in pSS patients are rare.[65–67] In a small series of patients with sensory ataxia who were studied with spinal cord MRI, high-intensity T2 abnormalities were found in the posterior columns of the cervical cord in 12 of 14 patients, 2 of whom had a necrotizing vasculitis.[68] Case reports of postmortem examination of a patient with recurrent transverse myelitis demonstrated angiitis and necrosis in the cervical and thoracic spinal cord but not elsewhere in the CNS.[69,70] Cerebral vasculitis is very rarely reported in pSS. In Alexander and colleagues' series,[71] focal clinical CNS disease was associated with brain infarcts and angiographic evidence of small vessel angiitis. MRI findings in patients with active CNS disease and SS are typically that of diffuse small foci of hyperintensity on T2-weighted imaging, suggestive of small vessel disease.

Small vessel disease can also lead to subtle cognitive dysfunction and result in impairment in attention and executive function, typically with preservation of memory. However, vasculopathy is unlikely to be the only mechanism leading to cognitive dysfunction in patients with pSS. Cognitive impairment is also detected in the absence of MRI abnormalities suggestive of vascular lesions in pSS. Single photon emission computed tomography imaging of pSS patients with normal brain MRI and neuropsychiatric involvement demonstrated lesions compatible with cerebral hypoperfusion in 56%.[72] Based on this study, it seems likely that pathogenic mechanisms other than

vasculopathy will be found in as many as 45% of SS patients with CNS involvement, particularly those with subtle cognitive impairment.

Pathogenic Autoantibodies

Autoantibodies potentially contribute to neuropathology by a variety of mechanisms, including immune complex mediated vasculitis, direct targeting of surface antigen leading to injury to myelin or neuronal tissue, and targeting of postganglionic receptors by functional autoantibody. Antiphospholipid antibodies (aPL) are associated with stroke, migraine, seizures, and transverse myelitis.[73] Although described in 5% to 14% of pSS patients, aPL antibody seems not to be associated with CNS disease in pSS.[9,74,75] However, a single small study suggested a possible role for aPL antibody in hearing loss in pSS. Clinically significant sensorineural hearing loss was found in 5 of 30 women and hearing loss correlated with the presence of anticardiolipin antibodies.[76] Patients with pSS and CNS disease have not been found to have evidence of antineuronal antibodies or antiribosomal antibodies. Neither antibody was found in paired serum/CSF samples from patients with active CNS-SS, suggesting that different immunopathologic mechanisms are responsible for CNS disorders in SLE and pSS.[21]

Whether anti-Ro/SSA has a direct pathophysiologic role in mediating vasculopathy resulting in neuronal damage remains speculative, despite previous studies that linked anti-Ro/SSA antibody to vasculopathy in both SLE and pSS.[77,78] In Western blot experiments using human umbilical vein endothelial cells, sera containing anti-Ro/SSA antibodies from patients with CNS-SS bound to 50 out of 54 and 60-kDa peptides, providing support for the hypothesis that anti-Ro/SSA antibodies bind to brain endothelial cells and play a role in the inflammatory process.[71] Ro52 expression was recently shown to be localized and highly enriched in the brain microvascular compartment in a recent study that used bovine brain tissue.[79] The mechanism by which circulating IgG might interact with brain endothelial Ro52 is unclear. A single report described three patients with pSS in whom cerebrospinal fluid anti-Ro/SSA antibody was detected along with intrathecal IgG synthesis.[80] Demonstration for the first time of intrathecal anti-Ro/SSA synthesis in two out of three patients with pSS who had CNS manifestations suggests that even in the absence of disruption of the blood brain barrier, anti-Ro/SSA may play a role in mediating CNS disorders.

Sera positive for antibody to extractable nuclear antigens (ENA) based on enzyme immunoassay, despite negative antinuclear antibodies, were recently studied and the associated clinical characteristics reported by Davis and colleagues.[81] Neurologic disorders, specifically peripheral neuropathy, were the predominant manifestation. The autoantibodies detected by ENA were anti-Ro/SSA or anti-La/SSB (in 33 out of 39 patients), with a minority of sera positive for U1 RNP or Scl -70. The neurologic manifestations based on retrospective chart review were sensorimotor polyneuropathy, small fiber neuropathy, ataxia, sensory neuronopathy, and progressive dementia with seizure disorder, a profile very similar to that described in neurologic SS.

Recently, a novel family of autoantibodies directed against cytoplasmic antigens has been added to the family of RNA-binding autoantibodies detectable in sera from patients with SS and other autoimmune disorders. GW/P antibodies target cytoplasmic structures that are involved in mRNA processing, RNA interference, and mRNA degradation. Proteins targeted by GW/P antibodies contain a glycine/tryptophan rich mRNA-binding sequence.[82] Preliminary data from a single study have suggested that the clinical presentations most commonly associated with seropositivity to GW body epitopes are neurologic disorders. Selection of sera reactive against GW body autoantigens identified a cohort of 55 patients with a mean age of 61, the

majority of whom had SS and neurologic disease.[83] The most common clinical presentation, based on retrospective review of 42 patients in whom clinical data was available, was neurologic in 33% (ataxia, motor, and sensory neuropathy). Interestingly, 44% of the patients with anti-GWB had reactivity to Ro52 as well. Other autoimmune diseases associated with GW/P reactivity in less than 15% of the patients included SLE, primary biliary cirrhosis, RA, and MS.

Aquaporin (AQP) family proteins are differentially distributed in endovascular and neuronal tissue throughout the central and peripheral nervous system. Abnormal distribution of AQP in the salivary and lacrimal glands has been described in pSS.[84,85] Increasing evidence also suggests that autoantibodies directed against AQPs mediate neurologic disease. A unique association of antibody directed against AQP4, a member of the family of water channel proteins, has been described in association with neuromyelitis optica. The histopathology of NMO is that of both necrotizing vasculitis and demyelination, which by definition extends over three or more segments of spinal cord. Immunohistologic examination of spinal tissue has demonstrated deposition of NMO antibody,[86] which detects clinically-defined NMO with high sensitivity and specificity.[87] Elegant immuno-histochemical studies by Lennon and colleagues[88] demonstrated that AQP4 is the autoantigen targeted by NMO-positive sera, providing evidence of an autoimmune ''channelopathy,'' although the precise mechanism whereby autoimmunity to AQP4 results in the restricted immunopathology of NMO is yet to be clarified. Patients with classic MS are uniformly sero-negative for NMO antibody.[87]

A variety of mechanisms have been explored in animal models, which suggest a role for AQP autoantibodies in mediating neurologic disorders. AQP1 is expressed in the CNS in the trigeminal nucleus, the retina, and the choroid plexus epithelial cells. Both AQP1 and AQP4 are expressed in dorsal root ganglia. Within the dorsal root and trigeminal sensory ganglia, AQP1 is concentrated in small diameter cell bodies, which give rise to unmyelinated C-fibers. Deletion of AQP1 in mice is associated with decreased response to pain and thermal stimuli, suggesting the possibility that antibody targeting AQP could have a functional role in modulating nociception.[89] An immune role in mediating neuropathic pain in SS is suggested by the observation that lymphocyte infiltration of dorsal root ganglia can be a histologic feature of sensory neuronopathy, and the demonstration that inflammation of neuronal tissue can result in activation of microglia and lead to expression of inflammatory cytokines that potentially mediate neuronal injury.[90,91]

Of additional interest are studies of salivary gland function, suggesting that stimulation of the muscarinic 3 receptor (M3R) found in salivary gland tissue results in translocation of AQP5 from the basal to apical plasma membrane of salivary myoepithelial cells.[92] The inhibitory effect of SS IgG on the expression of AQP5 has been examined in a model using rat parotid acinar cells and pilocarpine-induced AQP5 trafficking to the apical membrane. After incubating the cells for 12 hours with SS IgG, compared with control sera, Calcium mobilization, and AQP5 trafficking was reduced, suggesting a possible mechanism whereby antibody directed against AQP5 might mediate autonomic dysfunction.[93]

Antibodies against cholinergic receptors have attracted considerable interest as potential mediators of parasympathetic nervous system dysfunction in SS.[94] M3R is restricted to expression in peripheral autonomic organs, with the highest expression in salivary gland and smooth muscle cells.[95] Recent work from several groups using a variety of techniques including immunohistochemistry and Western blotting,[96] radioligand binding,[97,98] enzyme-linked immunosorbent assay (ELISA),[99] and bioassay have suggested the presence of autoantibody in pSS IgG that recognize

M3R.[100,101] Animal studies have suggested a role for antibody-targeting cell surface M3 signal transduction receptor as a primary event in autoimmune exocrinopathy.[102] Passive transfer experiments in NOD/SCID mice and in vitro studies with a muscarinic agonist provide evidence for a negative effect on the secretory response of submandibular gland cells treated with anti-M3 receptor antibody.[103]

The putative role of antibodies to the acetylcholine receptor as a mediating of autonomic neuropathy in pSS was investigated by Waterman and colleagues.[104] IgG autoantibody found in patients with both primary and secondary SS induces cholinergic hyper-responsiveness and detrusor instability on passive transfer to normal mice potentially through, compensatory up-regulation of postsynaptic M3R receptor number, consistent with the hypothesis that the overactive bladder in pSS is an autoantibody mediated disorder.[101] Proof of a pathogenic role for anti-M3R antibody in autonomic dysfunction in pSS will require purification and characterization of the antibody. Conventional immunologic techniques have not confirmed detectable binding of pSS IgG to M3R, and studies to date have relied on biologic assays that have proven difficult to replicate.[105] The most compelling evidence for functional M3R antibody in pSS remains a bioassay capable of detecting circulating antibody at concentrations below the nanogram threshold for detection of antibody using whole-cell ELISA or immunoblotting.[105] Recently, it was reported that an unusual low affinity muscarinic receptor blocking antibody detectable in picogram concentrations in sera was detectable by bioassay in the majority of patients with pSS and in patients with scleroderma.[100] Passive transfer experiments demonstrated functional properties in a biologic preparation in exceedingly low concentrations. Treatment with intravenous immunoglobulin (IVIG) prevented the functional consequences. Demonstration of the clinical relevance of anti-M3 receptor antibody will require development of a standardized assay for detection of antimuscarinic receptor antibody.

Inflammatory Mediators

The known CNS effects of inflammatory cytokines regulated by interferon include behavioral disturbances. For example, interleukin (IL)-1 can induce slow-wave sleep, loss of appetite, and enhanced production of corticotrophin releasing hormone (CRH). In patients with hepatitis C infection (HCV), the severity of depressive symptoms is correlated with expression of proinflammatory cytokines.[106] A variety of inflammatory cytokines and chemokines, including IL2, IL6, IL10, interferon-alpha (IFN-α), and tumor necrosis factor-alpha, as well as metalloproteinase-9, are potential triggers of neuronal cell activation.[107] Intrathecal production of proinflammatory cytokines could be stimulated by locally produced or circulating autoantibodies, and peripherally generated cytokines may mediate behavioral symptoms through passage of cytokines through leaky regions in the blood-brain barrier or through active transport and transmission of cytokine signals via afferent nerve fibers.[108]

Studies of autoimmune disease in animal models have suggested a pathogenic role for both autoantibody production and intrathecal production of inflammatory cytokines in the pathogenesis of nervous system disorders.[109] Behavioral changes and cognitive dysfunction are well described in several animal models of spontaneous autoimmune disease.[110–112] The deficits in hippocampal learning and memory, which occur in autoimmune mice, are similar to the cognitive disturbances found in patients with SLE and SS.[113,114] In the animal models of chronic autoimmune disease, cognitive dysfunction develops early in the absence of gross CNS damage.[112,113] Up-regulation of the hippocampal immune system, resulting in microglial production of inflammatory cytokines, has been demonstrated in mice with spontaneous autoimmune disease.[115] In animals, chronic inflammatory stress results in damage to

hippocampal neurons, as does anti-DNA antibody, which preferentially binds to hippocampal neurons and causes neuronal death with resulting cognitive dysfunction.

IFN-α administration is commonly associated with a spectrum of neuropsychologic effects, including fatigue, vegetative symptoms (sleep disorder, psychomotor slowing, and anorexia), and affective disorders (anxiety and depression), in addition to cognitive effects and profound cerebral dysfunction. In cancer patients undergoing IFN-α therapy, a well described syndrome of IFN-mediated fatigue followed by depression occurs and progresses to coma if INF-α therapy is continued.[116] A similar syndrome of fatigue, cognitive dysfunction, and depression is associated with IFN-α therapy of chronic hepatitis C liver disease.[117]

The psychopathology associated with interferon treatment is hypothesized to be in part mediated by pro-inflammatory cytokines (IL-1, IL-6) induced by IFN-α.[118] Animal data support a role for IFN-α in mediating behavioral changes. IFN-α has effects on intracerebral proinflammatory cytokine production and activation of corticotrophin releasing factor (CRF) production, leading to dysregulation of the hypothalamic-pituitary-adrenal axis (HPA). In humans, acute administration of IFN-α robustly activates the HPA axis via enhanced production of CRF.[119] Additionally, it has been reported that those melanoma patients who develop major depression while undergoing IFN-α therapy have significantly higher responses of corticotropin and cortisol.[120] These data, however, are inconsistent with data regarding pituitary-adrenal axis function in pSS. Johnson and colleagues[121] assessed pituitary and adrenal function in eight pSS subjects with anxiety (seven out of eight) and depression (three out of eight) and eight healthy controls. Significantly lower corticotropin and cortisol levels, as well as a lack of response to CRH, was found in the pSS patients, suggesting hypofunction rather than hyperfunction of the HPA axis.

IFN-α is also hypothesized to mediate depression by enzymatic effects on the rate-limiting step of tryptophan (TRP) conversion into kynurenine, thereby reducing availability of TRP conversion into serotonin. Intra-cerebroventricular injection of IFN-α in animals results in depletion of TRP, the primary precursor of serotonin, and is correlated with depression.[122] Studies in human beings have demonstrated that INF-α induced changes in TRP metabolism are related to depression.[123] Serotonin and CRF pathways may converge in mediating mood and cognitive symptoms, as the vegetative and somatic symptoms during IFN-α treatment correlated with effects on CRF pathways, whereas mood and cognitive symptoms correlated with the magnitude of TRP depletion in plasma.[120]

Evidence linking IFN-α with neuropsychiatric symptoms in cancer and HCV suggests a potential role for interferon inducible inflammatory cytokines in mediating the cognitive and affective disorders in medically ill patients, particularly persons with rheumatic disorders; however, the data exploring the relationship between neuropsychiatric symptoms and IFN-α or inflammatory cytokines in autoimmune disease are very limited. Levels of IFN-α were increased in the CSF of five of six patients with lupus psychosis, and in four of these five patients, the levels in CSF were higher than those in serum. IFN-α levels decreased when the manifestations of lupus psychosis subsided.[124] Investigators in the Division of Rheumatic and Autoimmune disease at the University of Minnesota have demonstrated abnormal regulation of type I interferon (IFN-α) inducible genes in association with both SLE and with SS.[125,126] Three molecules in the inflammatory IL-1 cytokine pathway regulated by interferon were over-expressed: IL-1β, the IL-1 receptor, and the IL-1 receptor antagonist. One group recently reported that increased expression of the interferon gene signature in peripheral blood mononuclear cells correlates with anti-Ro/SSA antibody titer.[127] However, a recent study, which examined the relationship between fatigue and

concurrent immunologic status in pSS, did not support the hypothesis of a causative role for IFN-induced cytokines in that fatigue was equally prevalent among seronegative and seropositive patients.[31] Whether CSF levels of inflammatory cytokines are higher in pSS patients with vegetative symptoms or depression, or whether TRP concentrations are reduced in plasma of pSS patients with depression, is unknown.

Cellular Autoimmunity

Hypothetical mechanisms of cell-mediated autoimmunity of potential relevance to pSS are (1) imbalance between autoimmune effector and regulatory T cells and (2) genetically determined (ie, intrinsic) abnormality in T-cell activation, resulting in loss of tolerance to neural autoantigens. Histopathologic examination in patients with sensory neuronopathy has demonstrated mononuclear infiltration of dorsal root ganglia.[62,63] Electrophysiologic studies have tended to support the concept of a sensory ganglionopathy, specifically with involvement of the neuronal cell body as opposed to the axon or root in patients with SS and sensory neuronopathy. Activation of endogenous neuropeptides in nerve fibers, as well as up-regulated expression of neuropeptides in mast cells, plasma cells, and lymphocytes, has also been suggested as a possible mechanism of dorsal root ganglionopathy.[128,129]

DIAGNOSIS

Differential Diagnosis of Central Nervous System-Sjögren's Syndrome

A large differential diagnosis, including inflammatory, infectious, genetic, metabolic, and neoplastic disorders, must be considered in the evaluation of CNS manifestations accompanying pSS. Other primary neurologic disorders, including amyotrophic lateral sclerosis and Parkinson's disease, must occasionally be considered in the neurologic differential depending upon the clinical presentation. Evaluation for antiphospholipid antibody is necessary as primary antiphospholipid syndrome (APS) can mimic CNS-SS. In patients with acute or subacute encephalopathy, CSF examination is important to exclude the presence of CNS infection. CSF analysis is rarely indicated in patients who present with cognitive complaints and a normal neurologic examination; however, evaluation for intrathecal antibody production and oligoclonal bands is required if clinical neurologic evaluation is abnormal or MRI suggests MS. Patients with recurrent optic neuritis or longitudinally extensive transverse myelitis should be tested for NMO IgG.

Whereas CSF examination demonstrating oligoclonal bands is characteristic of MS, in patients with primary SS and MS-like disease, the presence of only one or two bands[46] is characteristic. Coexistence of peripheral neuropathy was reported by Alexander and colleagues[46] in 20% of pSS patients with MS-like disease, and the presence of systemic features, such as cutaneous vasculitis or myositis (described in 40%), suggests pSS rather than MS. Performance of an ocular examination and minor salivary gland biopsy may be indicated in patients with MS who report sicca symptoms or those who have anti-Ro or anti-La antibody, particularly if there is evidence of cutaneous or systemic vasculopathy, inflammatory myositis, or peripheral neuropathy.

Imaging studies

Brain MRI scans in pSS may be normal or may demonstrate increased intensities on T2-weighted images predominantly involving subcortical and periventricular white matter. The specificity of these T2 white matter foci is poor, and controlled studies are conflicted with regard to whether pSS patients have more of such lesions than matched controls.[38,39] MRI studies alone may be insufficient in differentiating between

pSS and MS, as periventricular and subcortical lesions are found in both conditions. In both CNS-SS and MS these abnormalities generally do not resolve with therapy. Techniques that are complimentary to conventional MR sequences may provide additional insights into pathophysiologic processes occurring in pSS. Applying modern quantitative measures of global and regional brain volume in pSS patients may provide insight into neurologic manifestations of the disease, and cognitive dysfunction in particular. Other unconventional MRI techniques that measure structural (diffusion tensor imaging, magnetization transfer imaging), biochemical (magnetic resonance spectroscopy), or physiologic (functional MRI) brain abnormalities have not yet been systematically studied in Sjögren's syndrome.

Angiography

Cerebral angiography is sometimes performed to exclude other causes of CNS disease, such as arteriovenous malformation, congenital aneurysms, and cerebrovascular disease.[130] Diffuse narrowing, irregularity, dilatation, and occlusion suggest vasculitis on angiographic imaging and help to differentiate MS from connective tissue disease in patients with multifocal CNS involvement.

Brain biopsy

In patients with progressive and rapidly deteriorating CNS syndromes, in whom the precise etiology is unclear, brain biopsy is occasionally necessary to rule out infection or neoplasm.[131]

Differential Diagnosis of Peripheral Nervous System Disorders

Peripheral neuropathy has numerous causes, including hereditary, toxic, metabolic, infectious, inflammatory, ischemic, and paraneoplastic disorders. The number of peripheral neuropathies for which an etiology cannot be found despite extensive evaluation ranges from 13% to 22%.[132,133] The differential diagnosis of peripheral neuropathy is significantly narrowed by a focused clinical assessment. Most toxic and metabolic neuropathies are length-dependent and initially sensory. Pure sensory neuropathies or neuronopathies can result from drug toxicity (eg, thalidomide, cisplatin, mega-dose pyridoxine), paraneoplastic syndromes, or nutritional deficiencies, as well as SS.[134]

Clinical Evaluation

Sensory neuronopathy presents with sensory deficits without weakness and is readily recognized when patients present with regional or asymmetric sensory symptoms (for example, sensory loss, often with neuropathic pain, in a region of a single limb that does not conform to a peripheral nerve or dermatomal distribution) with no clinical or electrodiagnostic evidence of motor involvement. Reflexes are characteristically reduced. Sensory neuronopathy may present in a symmetric, distal predominant pattern as well, but in such cases it may not be possible to distinguish sensory neuronopathy from a sensorimotor polyneuropathy in which sensory signs and symptoms predominate.

Patients who present with unexplained pure sensory or sensory-predominant neuropathy, particularly if the pattern is regional or asymmetric, should be evaluated for pSS. As many as 23% of patients with small fiber neuropathy may meet criteria for pSS.[8] Tests of salivary gland function and lacrimal gland function can be helpful, even if sicca symptoms are absent, as symptoms correlate poorly with the results of objective tests of gland function.[135,136] Patients with anti-Ro/SS-A or anti-La/SS-B, who are asymptomatic with respect to sicca symptoms, require a minor salivary gland biopsy to confirm or exclude the presence of histopathologic criteria for SS.[137]

Multifocal neuropathies, including mononeuritis multiplex, can result in sensory abnormalities in specific nerve or root distributions. Ischemic neuropathies often have pain as a prominent feature. Infarctions of the nerve fascicles induce multifocal acute axonal lesions as a result of multiple small-vessel occlusion in the vasa nervorum.[138] In patients with subacute asymmetric neuropathy in whom vasculitic pathology is suspected, evaluation for cryoglobulinemia, monoclonal gammopathy, infectious causes, and lymphoma, as well as evaluation for a paraneoplastic disorder and connective tissue disease including SS, is necessary before deciding on treatment.

Laboratory Evaluation of Peripheral Nervous System Disorders

Nerve biopsy

Patients who present with painful, asymmetric neuropathy, especially if the onset is acute or subacute, should be considered for nerve biopsy. Histopathology of nerve biopsy tissue can be particularly helpful in confirming a clinical diagnosis of vasculitis, as well as sarcoidosis, leprosy, and amyloid neuropathy. Complications include infection, poor wound healing, and painful dysesthesias. In patients with SS who are selected for nerve biopsy, the histopathologic findings include necrotizing vasculitis, lymphocytic vasculitis, and nonspecific perivascular inflammatory infiltrates. A recent retrospective study of 40 patients meeting criteria for pSS suggested that vasculitis was predictive of a clinical response to immunosuppressive therapy.[54]

Autonomic testing

Investigation of heart rate variation with respiration, heart rate response to standing or tilting, blood pressure response to sustained hand grip, and a measure of sympathetic skin response, can be helpful in providing objective evidence of autonomic insufficiency and can act as a measure of small-fiber function. The quantitative sudomotor axon reflex test (QSART) can identify sudomotor (sweating) dysfunction.

Intra-epidermal nerve fiber biopsy

Skin biopsy to evaluate intra-epidermal nerve fiber density is a sensitive and useful means of detecting small fiber loss in pSS.[139] Reduction in intra-epidermal nerve fiber density identifies an additional 10% of patients with small-fiber neuropathy beyond the percentage identified with QSART.[140] The procedure is less invasive than sural nerve biopsy and can be repeated to follow disease progression (**Fig. 2**).

THERAPEUTIC APPROACHES

Patients with sensory complaints should be followed and a trial of immunomodulatory treatment considered if the extent of involvement and rate of progression suggest active inflammation. In the majority of pSS patients in whom sensory deficits remain stable, management is symptomatic and principles of neuropathic pain management are recommended. Treatments with documented efficacy in other neuropathic pain states include tricyclics, gabapentin, pregabalin, duloxetine, high-dose venlaxifene, tramadol, opioids, and topical local anesthetic agents.[141] Lidocaine patches are effective without systemic side effects.[142]

There is only anecdotal evidence of improvement with immuno-modulatory therapy in acute or subacute sensory neuropathy or neuronopathy from pSS. In the cases of pure sensory neuronopathy described by Font and colleagues,[6] treatment with intravenous cyclophosphamide and corticosteroids stabilized one patient, while one patient improved after IVIG and corticosteroids. Twenty percent followed a quiescent course initially, with progressively more severe symptomatology after 2 to 4 years.

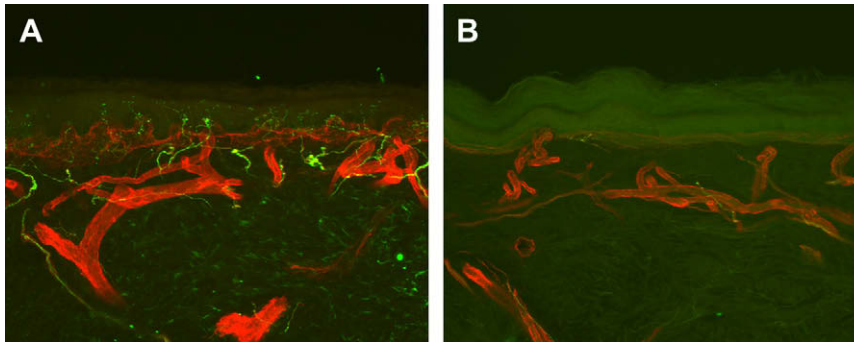

Fig. 2. (*A*) A normal subject. The horizontal red staining is collagen representing the epidermal basement membrane. Note the numerous and regularly arrayed epidermal nerves, stained with PGP 9.5 (*green*), a pan-neuronal marker, above the basement membrane. Nerves that contribute to the subepidermal neural plexus are seen below the basement membrane as well. (*B*) In the patient with small fiber neuropathy and pSS, virtually no nerves are identified. This is a relatively severe case of small fiber neuropathy.

Steroids and investigational therapies with biologic agents may be useful in those with subacute onset and progressive neurologic involvement. Treatment response to IFN-α was described in three cases of neuropathy, two with sensory ataxic ganglionopathy and one with sensorimotor neuropathy, reported by Yamada and colleagues.[143] In each case, neurologic symptoms which previously required repeated doses of IVIG for control remitted, salivary gland infiltration decreased, and sicca symptoms resolved after 3 MIU per day, three times weekly, for 2 months. Treatment of mononeuritis multiplex is directed against the specific underlying cause if identified. A specific viral cause excludes the diagnosis of pSS. Sjögren's syndrome patients with vasculitic neuropathy and cryoglobulinemia respond well to steroids and cyclophosphamide.[54] In patients with mononeuritis multiplex in whom cryoglobulinemia or lymphoma are not detected, the addition of other immunosuppressive therapies may be more beneficial than steroids alone, but support for the role of combination therapy is largely anecdotal.

Treatment of CNS demyelinating syndromes depends on the clinical scenario. A short course of high-dose corticosteroids (eg, methylprednisolone 1,000-mg intravenously or by mouth daily for 5 days) is first-line treatment for acute inflammatory attacks, such as optic neuritis or transverse myelitis. Plasmapheresis has been reported to improve the neurologic outcome for patients with acute attacks who do not respond to corticosteroids.[144] Intravenous immunoglobulin does not appear to be of benefit in acute attacks of CNS demyelination, at least in adults.[145–147] Treatment with cyclophosphamide in patients with pSS and myelopathy may produce stabilization or partial recovery.[4,148,149]

Patients with pSS and relapsing inflammatory and demyelinating CNS syndromes pose a therapeutic dilemma because of uncertainty about whether relapsing CNS manifestations are inherent to SS or, alternatively, reflect the presence of two concomitant diseases (eg, pSS and MS, or pSS and NMO). Prophylactic therapy for relapsing-remitting MS includes IFN-β, glatiramer acetate, and natalizumab. Prophylactic treatment of NMO involves long-term azathioprine, other immunosuppressive agents, or intravenous immunoglobulin.[150] None of these treatments have been systematically studied in patients meeting diagnostic criteria for both SS and MS, or both MS and NMO. In general, it seems reasonable to treat patients who meet diagnostic criteria

for MS or NMO with appropriate immunotherapy. Plasmapheresis has been reported to improve the neurologic outcome for patients who have severe extensive myelitis of recent onset.[151] In a single, open-label study of the effects of rituximab in NMO, six out of eight subjects treated with rituximab were relapse-free, and the median attack rate declined from 2.6 attacks per patient per year to zero. Treatment was well tolerated and disability ratings were significantly improved at follow-up.[152] Rituxamab has shown promise in both MS and NMO and clinical trials are ongoing.[152,153] Other B-cell targeted therapies that have promise for pSS include epratuzumab, which has been studied in a small randomized trial.[154] T-cell targeted therapies (abatacept, alefacept) are possible future options that have not as yet been explored for patients with severe neurologic involvement.

SUMMARY

Primary Sjögren's syndrome is a common illness in which diagnosis is frequently delayed. Neurologic disorders in the pSS population are associated with substantial reduction in quality of life. A major challenge for clinicians is the high percentage of SS patients whose experience of persistent abnormal fatigue, poorly characterized pain, cognitive symptoms, and affective disorders are not well understood. While biologic therapies appear promising, and conventional immunosuppressive regimens are useful in a small proportion of patients with severe neurologic manifestations, new approaches aimed at reducing neuronal damage and neuropathic pain are needed. More specific therapy for neuropsychologic symptoms is also urgently needed to ameliorate the burden of illness experienced by a large number of patients with pSS. In order to address the unmet health needs of the pSS population, a high priority for future research will be to asess whether neuropsychological symptoms in pSS represent a nonspecific response to chronic inflammatory disease or a manifestation of subtle nervous system involvement.

REFERENCES

1. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Arthritis Rheum 2008;58:15–25.
2. Carsons S. Sjögren's syndrome. In: Harris ED, Budd RC, Genovese MC, et al, editors. Kelly's textbook of rheumatology. Philadelphia: Elsevier Saunders; 2005. p. 1105.
3. Dafni UG, Tzioufas AG, Staikos P, et al. Prevalence of Sjögren's syndrome in a closed rural community. Ann Rheum Dis 1997;56:521–5.
4. Delalande S, de Seze J, Fauchais AL, et al. Neurologic manifestations in primary Sjögren's syndrome: a study of 82 patients. Medicine (Baltimore) 2004;83(5): 280–91.
5. Lafitte C, Amoura Z, Cacoub P, et al. Neurological complications of primary Sjögren's syndrome. J Neurol 2001;248:577–84.
6. Font J, Ramos-Casals M, de la Red G, et al. Pure sensory neuropathy in primary Sjögren's syndrome. Long-term prospective follow-up and review of the literature. J Rheumatol 2003;30(7):1552–7.
7. Mellgren SI, Conn DL, Stevens JC, et al. Peripheral neuropathy in primary Sjögren's syndrome. Neurology 1989;39(3):390–4.
8. Denislic M, Meh D. Early asymmetric neuropathy in primary Sjögren's syndrome. J Neurol 1997;244(6):383–7.

9. Govoni M, Bajocchi G, Rizzo N, et al. Neurological involvement in primary Sjögren's syndrome: clinical and instrumental evaluation in a cohort of Italian patients. Clin Rheumatol 1999;18:299–303.
10. Ramos-Casals M, Anaya JM, Garcia-Carrasco M, et al. Cutaneous vasculitis in primary Sjögren's syndrome: classification and clinical significance of 52 patients. Medicine (Baltimore) 2004;83(2):96–106.
11. Szanto A, Szodoray P, Kiss E, et al. Clinical, serologic, and genetic profiles of patients with associated Sjögren's syndrome and systemic lupus erythematosus. Hum Immunol 2006;67:924–30.
12. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European consensus group. Ann Rheum Dis 2002;61:544–8.
13. Belenguer R, Ramos-Casals M, Brito-Zeron P, et al. Influence of clinical and immunological parameters on the health-related quality of life of patients with primary Sjögren's syndrome. Clin Exp Rheumatol 2005;23:351–6.
14. Kabasakal Y, Kitapcioglu G, Turk T, et al. The prevalence of Sjögren's syndrome in adult women. Scand J Rheumatol 2006;35:379–83.
15. Kassan SS, Haralampos M, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren's syndrome. Arch Intern Med 2004;164:1275–84.
16. Manganelli P, Fietta P, Quaini F. Hematologic manifestations of primary Sjögren's syndrome. Clin Exp Rheumatol 2006;24:438–48.
17. Gudbjornsson B, Broman JE, Hetta J, et al. Sleep disturbances in patients with primary Sjögren's syndrome. Br J Rheumatol 1993;32:1072–6.
18. Barendregt PJ, Visser M, Smets E, et al. Fatigue in primary Sjögren's syndrome. Ann Rheum Dis 1998;57:291–5.
19. Tensing E, Solovieva SA, Tervahartiala T, et al. Fatigue and health profile in sicca syndrome of Sjögren's and non-Sjögren's syndrome origin. Clin Exp Rheumatology 2001;19:313–6.
20. Mauch E, Volk C, Kratzsch G, et al. Neurological and neuropsychiatric dysfunction in primary Sjögren's syndrome. Acta Neurol Scand 1994;89(1):31–5.
21. Spezialetti R, Bluestein HG, Peter JB, et al. Neuropsychiatric disease in Sjögren's syndrome: anti-ribosomal P and anti-neuronal antibodies. Am J Med 1993;95(2):153–60.
22. Malinow KL, Molina R, Gordon OA, et al. Neuropsychiatric dysfunction in primary Sjögren's syndrome. Ann Intern Med 1985;103:344–50.
23. Tishler M, Barak Y, Paran D, et al. Sleep disturbances, fibromyalgia and primary Sjögren's syndrome. Clin Exp Rheumatol 1997;15:71–4.
24. Valtysdottir ST, Gudbjornsson B, Lindqvist U, et al. Anxiety and depression in patients with primary Sjögren's syndrome. J Rheumatol 2000;27:165–9.
25. Valtysdottir ST, Gudbjornsson B, Hallgren R, et al. Psycholgical well-being in patients with primary Sjögren's syndrome. Clin Exp Rheumatol 2000;18:597–600.
26. Champey J, Corruble E, Gottenberg JE, et al. Quality of life and psychological status in patients with primary Sjögren's syndrome and sicca symptoms without autoimmune features. Arthritis Rheum 2006;55:451–7.
27. Escudero D, Latorre P, Codina M, et al. Central nervous system disease in Sjögren's syndrome. Ann Med Interne (Paris) 1995;146:239–42.
28. Belin C, Moroni N, Callat-Vigneron M, et al. Central nervous system involvement in Sjögren's syndrome: evidence from neuropsychological testing and HMPAO-SPECT. An Med Interna 1999;150:598–604.
29. Hietaharju A, Yli-Kerttula U, Hakkinen V, et al. Nervous system manifestations in Sjögren's syndrome. Acta Neurol Scand 1990;81:144–52.

30. Drosos AA, Andonopoulos AP, Lagos G, et al. Neuropsychiatric abnormalities in primary Sjögren's syndrome. Clin Exp Rheumatol 1989;7(2):207–9.
31. Segal B, Thomas W, Rogers T, et al. Prevalence, severity and predictors of fatigue in primary Sjögren's syndrome (Abstract, Suppl). Arthritis Rheum 2008; 59:in press.
32. Utset TO, Golden M, Siberry G, et al. Depressive symptoms in patients with systemic lupus erythematoussu: association with central nervous system lupus and Sjögren's sydrome. J Rheumatol 1994;21:2039–45.
33. Molina R, Provost TT, Alexander EL. Peripheral inflammatory vascular disease in Sjögren's syndrome. Arthritis Rheum 1985;28:1342–7.
34. Anaya JM, Villa LA, Restrepo L, et al. Central nervous system compromise in primary Sjögren's syndrome. J Clin Rheumatol 2002;8.189–96.
35. Archer HA, Macfarlane F, Price S, et al. Do symptoms of memory impairment correspond to cognitive impairment: a cross sectional study of a clinical cohort. Int J Geriatr Psychiatry 2006;21:1206–12.
36. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry 2000;5:983–91.
37. Reid LM, MacLullich AM. Subjective memory complaints and cognitive impairment in older people. Dement Geriatr Cogn Disord 2006;22:471–85.
38. Coates T, Slavotinek J, Rischmueller M, et al. Cerebral white matter lesions in primary Sjögren's sydrome: a controlled study. J Rheumatol 1999;26:1301–4.
39. Mataro M, Escudero D, Ariza M, et al. Magnetic resonance abnormalities associated with cognitive dysfunction in primary Sjögren's Syndrome. J Neurol 2003;250:1070–6.
40. Caselli RJ, Schneithauer BW, Bowles CA. The treatable dementia of Sjögren's sydrome. Ann Neurol 1991;98–101.
41. Moll JW, Markusse HM, Pijnenberg JJ, et al. Anti-neuronal antibodies in patients with neurologic complications of primary Sjögren's syndrome. Neurology 1993; 43:2574–81.
42. Pericot I, Brieva I, Tintore M, et al. Myelopathy in seronegative Sjögren's syndrome and/or progressive multiple sclerosis. Mult Scler 2003;9:256–9.
43. Wise CM, Agudelo CA. Optic neuropathy as an inital manifestation of Sjögren's syndrome. J Rheumatol 1988;15:799–802.
44. Rapoport P, Merle H, Smadja D. Ischemic choroidopathy in primary Sjögren's syndrome. Acta Ophthalmol Scand 1998;76(5):627–8.
45. Pittock SJ, Lennon VA, de Seze J, et al. Neuromyelitis optica and non-organ specific autoimmunity. Arch Neurol 2008;65:78–83.
46. Alexander EL, Makinow K, Lejewski JE, et al. Primary Sjögren's syndrome with central nervous system disease mimicking multiple sclerosis. Ann Intern Med 1986;104:323–30.
47. Wang Y, Tsai KY, Fuh JL, et al. High frequency of primary Sjögren's syndrome in Tawian presenting as relapsing-remitting multiple sclerosis. Eur Neurol 2004;51:21–5.
48. de Seze J, Devos D, Castelnovo G, et al. The prevalence of Sjögren's syndrome in patients with primary progressive MS. Neurology 2001;57:1359–63.
49. Noseworthy JH, Bass BH, Vandervoort MK, et al. The prevalence of primary Sjögren's syndrome in a multiple sclerosis population. Ann Neurol 1989;25:95–8.
50. Miró J, Peña-Sagredo JL, Berciano J, et al. Prevalence of primary Sjögren's syndrome in patients with MS. Ann Neurol 1990;27:582–4.

51. Metz LM, Seland TP, Fritzler MJ. An analysis of the frequency of Sjögren's syndrome in a population of multiple sclerosis patients. J Clin Lab Immunol 1989;30:121–5.
52. Weinshenker BG, Wingerchuk DM, Nakashima I, et al. OSMS is NMO, but not MS: proven clinically and pathologically. Lancet Neurol 2006;5:110–1.
53. Misu T, Fujihara I, Nakashima I, et al. Pure optic-spinal form of multiple sclerosis in Japan. Brain 2002;125:2460–8.
54. Terrier B, Lacroix C, Guillevin L, et al. Diagnostic and prognostic relevance of neuromuscular biopsy in primary Sjögren's syndrome related neuropathy. Arthritis Rheum 2007;57:1520–9.
55. Garcia-Carrasco M, Ramos Casals M, Rosas J, et al. Primary Sjögren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 2002;81:270–80.
56. Grant IA, Hunder GG, Homburger HA, et al. Peripheral neuropathy associated with sicca complex. Neurology 1997;48(4):855–62.
57. Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. Brain 2005;128:2518–34.
58. Andonopoulos AP, Lagos G, Drosos AA, et al. The spectrum of neurological involvement in Sjögren's syndrome. Br J Rheumatol 1990;29(1):21–3.
59. Gemignani F, Marbini A, Pavesi G, et al. Peripheral neuropathy associated with primary Sjögren's syndrome. J Neurol Neurosurg Psychiatr 1994;57(8):983–6.
60. Mochizuki H, Kamakura K, Masaki T, et al. Motor dominant neuropathy in Sjögren's syndrome: report of two cases. Intern Med 2002;41(2):142–6.
61. Goransson LG, Herigstad A, Tjensvoll AB, et al. Peripheral neuropathy in primary Sjögren's syndrome. Arch Neurol 2006;63:1612–5.
62. Griffin JW, Cornblath DR, Alexander E, et al. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjögren's syndrome. Ann Neurol 1990; 27(3):304–15.
63. Malinow K, Yannakakis GD, Glusman SM, et al. Subacute sensory neuronopathy secondary to dorsal root ganglionitis in primary Sjögren's syndrome. Ann Neurol 1986;20(4):535–7.
64. Segal B, Bowman SJ, Fox PC, et al. Prevalence of sensory symptoms in primary Sjögren's syndrome (PSS) and relationship of neuropathic symptoms to depression and fibromyalgia. Arthritis Rheum 2007;56(Suppl):S448.
65. Ranzenbach M, Kumar A, Rosenbaum A, et al. Anti-Ro(SS-A) autoantibodies (A-RoAb) in the immunopathogenesis of serious focal CNS disease in Sjögren's syndrome. Arthritis Rheum 1992;35(Suppl):114.
66. Alexander GE, Provost TT, Stevens MB, et al. Sjögren's syndrome: central nervous system manifestations. Neurology 1981;31:1391–6.
67. Alexander EL, Craft C, Dorsch C, et al. Necrotizing arthritis and spinal subarachnoid hemorrhage in Sjögren's syndrome. Ann Neurol 1982;11:632–5.
68. Mori K, Koike H, Misu K, et al. Spinal cord magnetic resonance imaging demonstrates sensory neuronal involvement and clinical severity in neuronopathy associated with Sjögren's syndrome. J Neurol Neurosug Psychiatry 2001;71:488–92.
69. Bakchine S, Duyckaerts C, Hassine L, et al. Central and peripheral neurologic lesions in primary Gougerot-Sjögren syndrome. Clinicopathological study of a case. Rev Neurol (Paris) 1991;147(5):368–75.
70. Giordano MJ, Commins D, Silbergeld DL, et al. Sjögren's cerebritis complicated by subarachnoid hemorrhage and bilateral superior cerebellar artery occlusion: case report. Surg Neurol 1995;43:48–51.

71. Alexander EL, Ranzenbach MR, Kumar AJ, et al. Anti-Ro autoantibodies in central nervous system disease associated with Sjögren's syndrome: clinical, neuroimaging, and angiographic correlates. Neurology 1994;44(5):899–908.
72. Chang C, Shiau Y, Wang J, et al. Abnormal regional cerebral blood flow on Tc ECD brain SPECT in patients with primary Sjögren's syndrome and normal findings on brain magnetic resonance imaging. Ann Rheum Dis 2002;61:774–8.
73. Muscal E, Brey RL. Neurological manifestations of the antiphospholipid syndrome: risk assessments and evidence-based medicine. Int J Clin Pract 2007;61:1561–8.
74. Cervera R, García-Carrasco M, Font J, et al. Antiphospholipid antibodies in primary Sjögren's syndrome: prevalence and clinical significance in a series of 80 patients. Clin Exp Rheumatol 1997;15(4):361–5.
75. Fauchais AL, Lambert M, Launay D, et al. Antiphospholipid antibodies in primary Sjögren's syndrome: prevalence and clinical significance in a series of 74 patients. Lupus 2004;13:245–8.
76. Tumiati B, Casoli P, Parmeggiani A. Hearing loss in the Sjögren's syndrome. Ann Intern Med 1997;126:450–3.
77. Alexander EL, Arnett F, Provost TT, et al. Sjögren's syndrome: association of anti-Ro(SS-A) antibodies with vasculitis, hematolgic abnormalities, and serologic hyperreactivity. Ann Intern Med 1983;98:155–9.
78. Simmons-O'Brien E, Chen S, Watson R, et al. One hundred anti-Ro(SSA) antibody positive patients: a 10 year follow-up. Medicine (Baltimore) 1995;74:109–30.
79. Shusta EV, Li JY, Boado RJ, et al. The Ro52/SS-A autoantigen has elevated expression at the brain microvasculature. Neuroreport 2003;14:1861–5.
80. Mégevand P, Chizzolini C, Chofflon M, et al. Cerebrospinal fluid anti-SSA autoantibodies in primary Sjögren's syndrome with central nervous system involvement. Eur Neurol 2007;57:166–71.
81. Davis JM, Moder KG, Homburger HA, et al. Clinical features of 39 patients with antibodies to extractable nuclear antigens despite negative antinuclear antibodies. Medicine (Baltimore) 2005;84:208–17.
82. Eystathioy T, Chan EKL, Tenebaum SA, et al. A phosphorylated cytoplasmic autoantigen, GW 182, associates with a unique population of human mRNAs within novel cytoplasmic speckles. Mol Biol Cell 2002;13:1338–51.
83. Bhanji RA, Eystathioy T, Chan EK, et al. Clinical and serological features of patients with autoantibodies to GW/P bodies. Clin Immunol 2007;125:247–56.
84. Steinfield S, Cogan E, King LS, et al. Abnormal distribution of aquaporin-5 water channel protein in salivary glands from Sjögren's syndrome patients. Lab Invest 2001;81:143–8.
85. Tsubota K, Hirai S, King LS, et al. Defective cellular trafficking of lacrimal gland AQP-5 in SS. Lancet 2001;357:688–9.
86. Lucchinetti CF, Mandeler RN, Avern D, et al. A role for humeral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain 2002;125:1450–61.
87. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364: 2106–12.
88. Lennon VA, Kryzer TJ, Pittock SJ, et al. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 2005;202:473–7.
89. Oshio K, Watanabe H, Yan D, et al. Impaired pain sensation in mice lacking aquaporin-1 water channels. Biochem Biophys Res Commun 2006;341(4): 1022–8.

90. Tanga FY, Nutile-McMenemy N, DeLeo JA, et al. The CNS role of toll-like receptor 4 in innate neuroimmunity and painful neuropathy. Proc Natl Acad Sci U S A 2005;102:5856–61.
91. Ledeboer A, Jekich BM, Sloane EM, et al. Intrathecal interleukin-10 gene therapy attenuates paclitaxel-induced mechanical allodynia and proinflammatory cytokine expression in dorsal root ganglia in rats. Brain Behav Immun 2007;21(5):686–98 [Epub 2006;21:686–98].
92. Konttinen YT, Tensing E, Laine M, et al. Abnormal distribution of aquaporin-5 in salivary glands in the NOD mouse model for Sjögren's syndrome. J Rheumatol 2005;32:1071–5.
93. Li J, Ha M, Kü NY, et al. Inhibitory effects of autoantibodies on the muscarinic receptors in Sjögren's syndrome. Lab Invest 2004;84:1430–8.
94. Hocevar A, Tomsic M, Praprotnik S, et al. Parasympathetic nervous system dysfunction in primary Sjögren's syndrome. Ann Rheum Dis 2003;62:702–4.
95. Nagaraju K, Cox A, Casciola-Rosen L, et al. Novel fragments of the Sjögren's syndrome autoantigens alpha-fodrin and type 3 muscarinic acetylcholine receptor generated during cytotoxic lymphocyte granule-induced cell death. Arthritis Rheum 2001;44:2376–86.
96. Bacman SR, Berra A, Sterin-Borda L, et al. Human primary Sjögren's syndrome autoantibodies as mediators of nitric oxide release coupled to lacrimal gland muscarinic acetylcholine receptors. Curr Eye Res 1998;17:1135–42.
97. Bacman S, Sterin-Borda L, Camusso JJ, et al. Circulating antibodies against rat parotid gland M3 muscarinic receptors in primary Sjögren's syndrome. Clin Exp Immunol 1996;104:454–9.
98. Robinson CP, Brayer J, Yamachika S, et al. Transfer of human serum IgG to nonobese diabetic Igmu null mice reveals a role for autoantibodies in the loss of secretory function of exocrine tissues in Sjögren's syndrome. Proc Natl Acad Sci U S A 1998;95:7538–43.
99. Bacman S, Berra A, Sterin-Borda L, et al. Muscarinic acetylcholine receptor antibodies as a new marker of dry eye Sjögren syndrome. Invest Ophthalmol Vis Sci 2001;42:321–7.
100. Dawson LJ, Stanbury J, Venn N, et al. Antimuscarinic antibodies in primary Sjögren's syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells. Arthritis Rheum 2006;54:1165–73.
101. Wang F, Jackson MW, Maughan V, et al. Passive transfer of Sjögren's syndrome IgG produces the pathophysiology of overactive bladder. Arthritis Rheum 2004; 50:3637–45.
102. Nguyen KH, Brayer J, Cha S, et al. Evidence for antimuscarinic acetylcholine receptor antibody-mediated secretory dysfunction in nod mice. Arthritis Rheum 2000;43(10):2297–306.
103. Smith AJ, Jackson MW, Wang F, et al. Neutralization of muscarinic receptor autoantibodies by intravenous immunoglobulin in Sjögren syndrome. Hum Immunol 2005;66:411–6.
104. Waterman SA, Gordon TP, Rischmueller M. Inhibitory effects of muscarinic receptor autoantibodies on parasympathetic neurotransmission in Sjögren's syndrome. Arthritis Rheum 2000;43:1647–54.
105. Dawson LJ, Allison HE, Stanbury J, et al. Putative anti-muscarinic antibodies cannot be detected in patients with primary Sjogren's syndrome using conventional immunological approaches. Rheumatology (Oxford) 2004;43:1488–95.

106. Loftis JM, Huckans M, Ruimy S, et al. Depressive symptoms in patients with chronic hepatitis C are correlated with elevated plasma levels of interleukin-1beta and tumor necrosis factor-alpha. Neurosci Lett 2008;430:264–8.
107. Pitossi F, del Rey A, Kabiersch A, et al. Induction of cytokine transcripts in the central nervous system and pituitary following peripheral administration of endotoxin to mice. J Neurosci Res 1997;48:287–98.
108. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci 2002;25:154–9.
109. Ferrari CC, Depino AM, Prada F, et al. Reversible demyelination, blood-brain barrier breakdown, and pronounced neutrophil recruitment induced by chronic IL-1 expression in the brain. Am J Pathol 2004;165:1827–37.
110. Forster MJ, Popper MD, Retz KC, et al. Age differences in acquisition and retention of one-way avoidance learning in C57BL/6NNia and autoimmune mice. Behav Neural Biol 1988;49(2):139–51.
111. Vogelweid CM, Wright DC, Johnson JC, et al. Evaluation of memory, learning ability and clinical neurologic function in pathogen-free mice with systemic lupus. Arthritis Rheum 1994;37:889–97.
112. Hess DC, Taormina M, Thompson J, et al. Cognitive and neurologic deficits in the MRL/lpr mouse: a clinicopathologic study. J Rheumatol 1993;20:610–7.
113. Sakic B, Szechtman H, Keffer M, et al. Neurobehavioral alteration in autoimmune mice. Neurosci Biobehav Rev 1993;21:327–40.
114. Walker S, Wright DC, O'Sullivan FX, et al. Memory, learning ability, and neuropathologic status of mice with systemic lupus erythematosus. Ann NY Acad Sci 1997;823:107–15.
115. Tomita M, Holman BJ, Santoro TJ. Aberrant cytokine gene expression in the hippocampus in murine systemic lupus erythematosus. Neurosci Lett 2001; 302:129–32.
116. Malik UR, Makower DF, Wadler S. Interferon-mediated fatigue. Cancer Pract 2001;92:1664–8.
117. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut 2006;55:1350–9.
118. Dantzer R, Wollman EE, Yirmiya R. Cytokines, stress, and depression. New York: Plenum, Kluwer Academic; 1999.
119. Capuron L, Raison CL, Musselman DL, et al. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. Am J Psychiatry 2003;160: 1342–5.
120. Capuron L, Miller AH. Cytokines and psychopathology: lessons from interferon-alpha. Biol Psychiatry 2004;56:819–24.
121. Johnson EO, Vlachoyiannopoulos PG, Skopouli FN, et al. Hypofunction of the stress axis in Sjögren's syndrome. J Rheumatol 1998;35:1508–14.
122. Kamata M, Higuchi H, Yoshimoto M, et al. Effect of single intracerebroventricular injection of alpha-interferon on monoamine concentrations in the rat brain. Eur Neuropsychopharmacol 2000;10:129–32.
123. Capuron L, Neurauter G, Musselman DL, et al. Interferon-alpha-induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. Biol Psychiatry 2003;54:906–14.
124. Shiozawa S, Kuroki Y, Kim M, et al. Interferon-alpha in lupus psychosis. Arthritis Rheum 1992;35(4):417–22.
125. Baechler EC. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci 2003;100:2610–5.

126. Grandits M, Machado DB, Meyer CM, et al. Identification of differential gene expression patterns in Sjögren's syndrome patients. American College of Rheumatology Annual Scientific Meeting. Arthritis Rheum 2002;46:S598.
127. Emamian ES, Leon J, Rao S, et al. Over-expression of interferon-inducible genes is highly correlated with sicca manifestations and autoantibody levels in Sjögren's syndrome. Arthritis Rheum 2004;50.
128. Joachim RA, Kuhlmei A, Dinh QT, et al. Neuronal plasticity of the "brain-skin connection": stress-triggered up-regulation of neuropeptides in dorsal root ganglia and skin via nerve growth factor-dependent pathways. J Mol Med 2007;85: 1369–78.
129. Batbayar B, Nagy G, Kovesi G, et al. Morphological basis of sensory neuropathy and neuroimmunomodulation in minor salivary glands of patients with Sjögren's syndrome. Arch Oral Biol 2004;49(7):529–38.
130. Soliotis FC, Mavragani CP, Moutsopoulos HM. Central nervous system involvement in Sjögren's syndrome. Ann Rheum Dis 2004;63:616–20.
131. Alexander EL. Neurologic disease in Sjögren's syndrome: mononuclear inflammatory vasculopathy affecting central/peripheral nervous system and muscle. Rheum Dis Clin North Am 1993;19:869–905.
132. Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. Ann Neurol 1981;10:222–6.
133. McLeod JG, Tuck RR, Pollard JD, et al. Chronic polyneuropathy of undetermined cause. J Neuro Neurosug Psychiatry 1984;47:530–5.
134. Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Philadelphia: Saunders; 1993.
135. Greenspan JS, Daniels TE, Talal N, et al. The histopathology of Sjögren's syndrome in labial saliary gland biopsies. Oral Surg Oral Med Oral Pathol 1974;37:217–29.
136. Andoh Y, Shimura S, Sawai T, et al. Morphometric analysis of secretory glands in SS. Am Rev Respir Dis 1993;148:1358–62.
137. Gorson KC, Ropper AH. Positive salivary gland biopsy, Sjögren's syndrome, and neuropathy: clinical implications. Muscle Nerve 2003;28(5):553–60.
138. Peyronnard JM, Charron L, Beaudet F, et al. Vasculitic neuropathy in rheumatoid disease and Sjögren's syndrome. Neurology 1982;32(8):839–45.
139. Chai J, Herrmann DN, Stanton M, et al. Painful small-fiber neuropathy in Sjögren's syndrome. Neurology 2005;65:925–7.
140. Mendell JR, Sahenk Z. Painful sensory neuropathy. N Engl J Med 2003;27: 1243–55.
141. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237–51.
142. Galer BS, Rowbotham MC, Von Miller K, et al. Treatment of inflammatory, neuropathic and sympathetically maintained pain in a patient with Sjögren's syndrome. Pain 1992;50(2):205–8.
143. Yamada S, Mori K, Matsuo K, et al. Interferon alpha treatment for Sjögren's syndrome associated neuropathy. J Neurol Neurosurg Psychiatr 2005;76:576–8.
144. Greenberg BM, Thomas KP, Krishnan C, et al. Idiopathic transverse myelitis: corticosteroids, plasma exchange, or cyclophosphamide. Neurology 2007;68: 1614–7.
145. Visser LH, Beekman R, Tijssen CC, et al. A randomized, double-blind, placebo-controlled pilot study of IV immune globulins in combination with IV methylprednisolone in the treatment of relapses in patients with MS. Mult Scler 2004;10: 89–91.

146. Roed HG, Langkilde A, Sellebjerg F, et al. A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. Neurology 2005;64:804–10.
147. Sorensen PS, Haas J, Sellebjerg F, et al. IV immunoglobulins as add-on treatment to methylprednisolone for acute relapses in MS. Neurology 2004;63(11): 2028–33.
148. Williams CS, Butler E, Roman GC. Treatment of myelopathy in Sjögren's syndrome with a combination of prednisone and cyclophosphamide. Arch Neurol 2001;58(5):815–9.
149. De Seze J, Delalande S, Fauchais AL, et al. Myelopathies secondary to Sjögren's syndrome: treatment with monthly intrvenous cyclophosphamide associated with corticosteroids. J Rheumatol 2006;33:709–11.
150. Papeix C, Vidal JS, de Seze J, et al. Immunosuppressive therapy is more effective than interferon in neuromyelitis optica. Mult Scler 2007;13:256–9.
151. Konttinen YT, Kinnunen E, von Bonsdorff M, et al. Acute transverse myelopathy successfully treated with plasmapheresis and prdnisone in a patient with primary Sjögren's syndrome. Arthritis Rheum 1987;30:339–44.
152. Cree B. Emerging monoclonal antibody therapies for multiple sclerosis. Neurologist 2006;12:171–8.
153. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008;358:676–88.
154. Steinfeld SD, Tant L, Burmester GR, et al. Epratuzumab (humanised anti-CD22 antibody) in primary Sjögren's syndrome: an open-label phase I/II study. Arthritis Res Ther 2006;8:R129.

Pulmonary Manifestations of Primary Sjögren's Syndrome

Ann L. Parke, MD

KEYWORDS

- Sjögren's syndrome • Interstial lung disease
- Lymphocytic interstial pneumonia
- Nonspecific interstial pneumonia
- Usual interstial pneumonia • Lymphoma

Even though the current classification criteria for Sjögren's syndrome (SS) includes subjective complaints of and objective findings for, xerophthalmia (dry eye) and xerostomia (dry mouth),[1] it generally is accepted that SS is in fact a systemic autoimmune disease with the potential to affect other exocrine glands and extraglandular tissues.[2–5] SS is a particularly interesting syndrome, because it is known to occur alone (primary SS) or in association with other autoimmune disease states(ie, organ-specific diseases [thyroid disease, primary biliary cirrhosis, Addison's disease, myasthenia gravis]), and less organ- specific systemic autoimmune diseases (ie, systemic lupus erythematosus [SLE], rheumatoid arthritis, systemic sclerosis, and undifferentiated overlap syndromes). SS associated with other connective tissues diseases is known as secondary SS.

SS has been referred to as an autoimmune exocrinopathy,[6] an autoimmune epithelitis,[7] and now is considered by some to be an SLE-like disease of the exocrine glands/mucus membranes.[8] Recent evidence has suggested that the glandular epithelial cells play a critical role in contributing to the pathogenesis of this disease.[9–15] The glandular epithelial cells found in patients who have SS are immunologically activated, expressing major histocompatibility (MHC) class 1 and 2 molecules[11,12] and B7 costimulatory molecules.[13] They also produce proinflammatory cytokines[14] and chemokines that attract lymphocytes,[15] suggesting that it is the epithelial cells that attract lymphocytes into the affected glands producing the characteristic peri-ductal focal lymphocytic infiltrate with T helper cells, B cells, and plasma cells found in SS.[16] The initiating event that stimulates the activation of these glandular epithelial cells is unknown, but many authors have suggested that persistent viral infections may play an important role in the pathogenesis of this disease.[17–20] Chronic HIV infection and chronic hepatitis C

Division of Rheumatology, Saint Francis Hospital and Medical Center, 114 Woodland Street, Hartford, CT 06105 1208, USA

Rheum Dis Clin N Am 34 (2008) 907–920
doi:10.1016/j.rdc.2008.08.012 rheumatic.theclinics.com
0889-857X/08/$ – see front matter

infection can produce a glandular pathology that is very similar to that found in idiopathic SS, and these virally infected patients may have complaints of dryness and glandular swelling.[21–24] Because chronic hepatitis C and HIV can produce falsely positive lip biopsies they are listed as exclusion criteria in the most recent classification criteria for SS.[1]

As epithelial cells line the entire respiratory system, it is not surprising that patients who have SS may present with various respiratory complaints and that in some instances these complaints may precede the more classical manifestations of SS.[25,26]

SS is also a lymphocyte aggressive disease with the infiltration of T and B cells into affected tissues. This dysregulated lymphocyte proliferation initially contains T helper cells (CD4), B cells, and plasma cells,[11,27,28] but in a small percentage of patients, it may continue in an unregulated fashion to develop into frank lymphoma,[29–31] another interesting aspect of SS. Initially, these infiltrating lymphocytes recognize boundaries but still can produce substantial tissue pathology by damaging glandular acini, biliary ducts, and renal tubules, and by obstructing small airways and producing interstitial lung disease (ILD).

The many pulmonary manifestations of SS are listed in **Boxes 1** and **2**, and it is probable that pulmonary disease occurs more commonly in patients who have SS than generally is accepted.

Data on the prevalence of pulmonary disease in patients who have SS are confusing. This is primarily because:

- The criteria for the classification of SS have changed, and exclusionary criteria have been added.
- Previous studies have failed to separate out patients who have primary or secondary disease.
- Various methods have been used to select patients and to test respiratory function.

Some reports have suggested that as many as 75% of patients who have primary SS may have respiratory manifestations.[32] Another study, however, compared

Box 1
Pulmonary disease in patients with primary Sjögren's syndrome

Anatomic classification

Airway disease
- Large airways; sicca of the large airways
- Lower airways; mild obstructive airway disease

Parenchymal disease
- ILD
- Interstitial damage: cysts, bullae, and fibrosis
- Pulmonary nodules

Pleural disease
- Rare in primary SS

Vascular disease
- Pulmonary hypertension, rare in primary SS
- Vasculitis

Box 2
Pulmonary disease in patients with primary Sjögren's syndrome

Pathologic classification

Airways

- Sicca of the airways and related nasal passages
- Bronchitis and bronchiolitis

Interstitial lung disease

- Lymphocytic interstitial pneumonia (LIP)
- Nonspecific interstitial pneumonia (NSIP)
- Usual interstitial pneumonia (UIP)

Lymphoproliferative disease

- Follicular lymphocytic infiltration:
  - Bronchial/bronchiolar
  - Interstitial/alveolar
- Pseudolymphoma
- Lymphoma (nodal and extra nodal)
- Amyloidosis

patients who had primary disease with patients who had secondary disease, with patients who had rheumatoid arthritis alone without SS and with normal controls. It determined that pulmonary abnormalities found in patients who have SS are not significant and clinically negligible when compared with a control population.[33] The consensus of opinion is that patients who have secondary disease are more likely to have severe disease, and the pattern of pulmonary disease in patients who have secondary diseases is also different,[33,34] which should not be surprising, as the underlying primary diseases also may contribute to pulmonary pathology. For example, patients who have secondary SS may present with pleural disease, which rarely is found in patients who have primary disease.[35] These additional complaints, however, are more likely to be a feature of the underlying primary connective tissue disease rather than the associated SS. The presence of a pleural effusion or hilar adenopathy in a patient who has primary SS should raise the possibility of lymphoma in that patient.[36] Some studies have suggested that specific clinical features and serologic features do not appear to predispose patients who have SS to particular pulmonary complaints except that patients who also have Raynaud's phenomenon are more likely to have more severe impairment of diffusion capacity.[34] Other studies, however, have determined that the presence of Ro antibody predisposes patients to develop extraglandular manifestations, including pulmonary disease.[37]

This article is limited to the pulmonary complaints found in patients who have primary disease.

AIRWAY DISEASE

The respiratory system starts at the nose and includes the associated nasal cavities. The nose is lined with hairs that filter the incoming air, trapping unwanted particles, and secretions from the nasal columnar epithelial cells help to moisten and remove

these inhaled particles. Reduced secretions from these epithelial cells can result in nasal crusting, epistaxis, and recurrent sinusitis.

Further down the airways, dryness in the trachea can produce a dry irritating nonproductive cough and dyspnoea.[38–40] Dry cough alone has been reported in up to 50% of primary patients who have SS,[38] even in the absence of radiographic changes or abnormal pulmonary function tests.[41] An autopsy study of six patients who had cough and SS demonstrated the presence of hyperplasia of submucosal glands and secretory cells without exocrine gland destruction.[42] A study of endobronchial biopsies demonstrated that compared with control subjects, patients with SS have an increased number of CD4-positive T cells in the lamina propria outside of the bronchial submucosal glands.[43] Lymphocytic infiltration in and around bronchi and bronchioles does not appear to increase the rate of infection, but it may lead to bronchial hyperreactivity[44] and small airway obstruction, considered by many to be one of the most common pulmonary manifestations occurring in patients who have SS.[34,38] Marked lymphocytic hyperplasia also may result in airway obstruction that is severe enough to produce a valve-like phenomenon that contributes in the development of cysts and bullae in some patients.[45–47]

INTERSTITIAL LUNG DISEASE

ILD can be a manifestation of pulmonary disease in various connective tissue diseases.[48] In some patients, the lung disease may be an initial presentation, occurring before the other more usual clinical complaints are apparent,[25,26] and it has been estimated that 15% to 20% of patients presenting with chronic ILD have an occult connective tissue disease,[49] whereas other studies have suggested that approximately 8% of primary SS patients have ILD.[50] Patients who have SS may develop various ILDs, and these patients typically present with cough, dyspnea, bilateral infiltrates on radiograph, and various patterns of abnormalities on high- resolution CT scan.[51] Several studies have determined that nonspecific interstial pneumonia (NSIP) is particularly prevalent in patients who have connective tissue diseases, and these results have suggested that a diagnosis of NSIP should suggest the presence of an underlying connective tissue disease.[52–54] Ito and colleagues[55] studied 33 patients who had primary SS and biopsy-proven lung disease (two were autopsy cases), and found that 20 (61%) of these patients had NSIP. Four had diffuse bronchiolitis, and four had non-Hodgkin's lymphomas of mucosal-associated lymphoid tissue (MALT) origin. Five patients also had evidence of amyloidosis, but none of these patients had evidence of lymphocytic interstial pneumonia (LIP), previously considered to be a characteristic interstitial pulmonary pathology for SS.[52]

LIP is considered to be a benign consequence of bronchus-associated lymphoid tissue (BALT) proliferation.[56] Lymphocytic infiltrates found on biopsy producing the histopathology of follicular bronchiolitis, lymphoid follicles, or LIP should suggest the presence of a connective tissue disease.[52] LIPs have been described as part of the spectrum of ILD found in approximately 1% of patients who have SS,[57,58] but although LIP is considered to be a steroid-responsive pathology, approximately 5% of patients who have LIP progress to develop overt lymphoma, and the 5 year mortality for these patients can be up to 50%.[56]

LIP also is found in patients who have HIV, and it is considered by some to be an AIDS-defining pathology in these patients.[59] A subset of patients who have HIV develop diffuse infiltrating lymphocytic syndrome (DILS), where the patients may develop parotid enlargement, lymphadenopathy, and sicca complaints[21] and have CD8 lymphocytic infiltration of salivary glands.[21,60] Approximately 50% of patients

who have DILS develop LIP.[61,62] This is particularly interesting, as all of these clinical and pathologic features are found in patients who have so-called idiopathic SS. Clearly these are both lymphocyte aggressive diseases, although the type of infiltrating lymphocyte is obviously different.

Idiopathic interstitial pneumonias (IIPs) recently have been reclassified, resulting in some LIPs now being classified as NSIPs depending on the degree of lymphocytic infiltration.[63]

Patients who have interstitial pulmonary fibrosis and a connective tissue disease are considered to have a better prognosis than those patients who have IIPs.[64–66] and this has been attributed to the higher frequency of NSIP found in patients who have an associated connective tissue disease. In an attempt to determine if this was indeed because of a higher frequency of NSIP occurring in connective tissue disease patients, Park and colleagues studied 362 patients who had fibrotic interstitial pneumonias (269 with IIP and 93 with an associated connective tissue disease). Patients who had known environmental exposures and patients who had cellular NSIP were excluded from the study. The results of this study again showed that the survival of patients who had fibrosing interstitial lung disease, in the presence of a connective tissue disease, was better than that found in IIP (131 months compared with 80.5 months).This difference primarily was because of the improved survival in patients who had UIP (177months versus 66.9 months), whereas there was no difference in survival between the two groups in patients who had fibrotic NSIP.[67]

LYMPHOMA

Patients who have SS are at risk for developing lymphomas, usually a low-grade, non-Hodgkin's MALT-associated lymphoma.[30,31,68–70] The low-grade nature of most of these tumors and the currently available treatment have led some to conclude that the diagnosis of a low-grade MALT lymphoma in a Sjögren's patient has no effect on longevity for that patient. Recent studies have determined that certain characteristics are predictive for developing lymphoma, and these include: a low C4, especially at the time of presentation,[71] recurrent glandular swelling, palpable purpura, and an elevated IgM.[71,72] Some authors have classified such patients as type 1 patients and have suggested that these patients merit close observation and monitoring for malignant change.[72]

Subepithelial aggregates of lymphoid tissue in bronchi and bronchioles have been labeled BALT.[73] The presence of BALT in normal human lung remains debated, but there is no doubt that this tissue can be induced under certain pathologic conditions, including: chronic lung infections, chronic viral infections, including HIV, and autoimmune conditions including SS.[73,74] Proliferation of BALT may result in peribronchial lymphoid hyperplasia, which can cause airway obstruction, one of the more common pulmonary manifestations of SS,[34,39,75] or alveolar interstitial LIP.

Unregulated BALT proliferation may result in malignant change with the development of primary pulmonary lymphoma.[76–78] Typically, Sjögren's patients who have developed primary pulmonary lymphoma present with minimal clinical complaints including cough, mild weight loss, and sometimes some shortness of breath.[78] By comparison, the radiographic studies are dramatic, with various findings including multiple bilateral infiltrates, multiple nodules, and micronodules. CT evaluation also reveals ground glass changes, air bronchograms, and thickening of the bronchial walls. One study of 10 primary pulmonary lymphoma patients, seven of whom had SS, revealed that none of these patients developed pleural effusions, calcifications, significant lymphadenopathy, or tumor necrosis.[78] Primary pulmonary lymphomas

are rare, but patients can develop pulmonary involvement as an extranodal manifestation of lymphomas occurring at other sites. All patients who have pulmonary findings warrant an extensive workup, including a tissue biopsy, CT of the abdomen, and bone marrow examination to determine extent of the disease.

OTHER PATHOLOGY

Pulmonary Hypertension

Pulmonary hypertension (PAH) is a rare complication of primary SS.[79–81] In a recent review by Launay and colleagues,[80] nine new cases were presented, and the 19 fully documented cases appearing in the English language literature were reviewed, although only 8 of these 19 other cases had a right heart catheterization, making a total of 17 patients with confirmed PAH. Exertional dyspnea was the initial symptom in 16 of the 17 patients, with syncope the initial complaint in the remaining patient. Mean time from initial complaint to diagnosis of PAH was 34.4 plus or minus 50.3 months, with delay in diagnosis of more than 1 year occurring in 69%. In the nine new cases described, Raynaud's syndrome occurred in 67%, cutaneous vasculitis in 33%, and ILD in 44%. All had antinuclear antibodies, and seven of the nine had antibodies to Ro antigen. Although phospholipid antibodies were not reported in all of these patients, 16 had ventilation/perfusion scans, with normal findings in 14, suggesting that thrombotic disease was probably not a primary cause of PAH in these 14 patients.[80]

The most worrisome findings in this report were that:
The PAH was severe at presentation in most cases.
Mean pulmonary artery pressure (mPAP) was 47 plus or minus 10 mm Hg.
Survival at 3 years was 83% for the nine new cases and 66% for the 17 cases in review.

Pulmonary pathology was available in six patients (five autopsy specimens) and revealed intimal and medial hypertrophy but no vasculitis or inflammatory infiltrate.[80] These findings suggest that prolonged vasospasm and vessel remodeling contributed significantly to the development of this pathology.

Amyloid

Pulmonary amyloid occurring in patients who have SS may present in various ways, including nodular pulmonary amyloidosis described in an SS patient treated with intermittent hemodialysis[82] Five of 33 cases of patients who had primary SS and who were studied by Ito and colleagues[55] demonstrated amyloid deposits on histologic examination, and three of these patients also had a primary pulmonary lymphoma. Similar findings were reported by Sugai[83] describing MALT lymphoma and primary amyloidosis in the lung in SS.

TESTS FOR EVALUATING PULMONARY DISEASE IN PATIENTS WITH SJÖGREN'S SYNDROME

Anatomic Tests

Chest radiographs may be abnormal even in patients who are asymptomatic. In a study comparing patients who had primary and secondary SS, some of whom were without significant pulmonary complaints, Vitali and colleagues[34] determined that approximately 27% of patients who had primary disease and 75% of patients who had secondary disease had abnormal chest radiographs. Chest radiographs, however, may not be particularly helpful for detecting subtle abnormalities in patients who have SS.[34,38,84] A study of 36 patients who had primary SS showed that 75% of

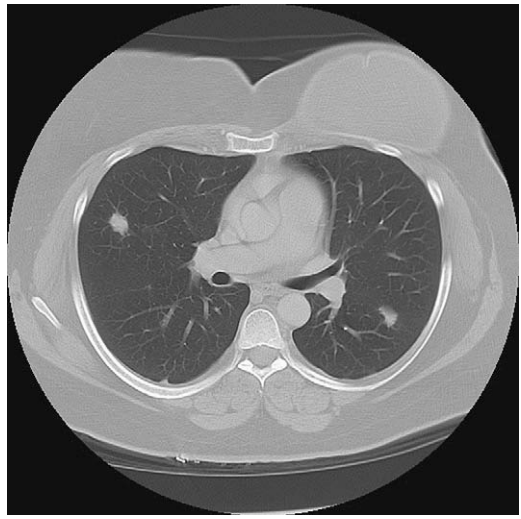

Fig. 1. A high-resolution chest CT with lung windows. Large bilateral soft tissue nodules without evidence of cavitation. Multiple nodules on other images are not shown. Nodules resolved completely when patient was treated with corticosteroids.

these patients had respiratory involvement occurring early in the disease. It also determined, however, that radiographs did not correlate with functional and histologic findings.[38]

High-resolution CT may be useful in detecting abnormalities, even in patients who are asymptomatic.[50,85] Uffman and colleagues[84] found that 65% of their asymptomatic Sjögren's patients had abnormal CT scans. The abnormalities demonstrated a predominance of lower lung zone pathology, particularly for inter- and intralobular thickening,

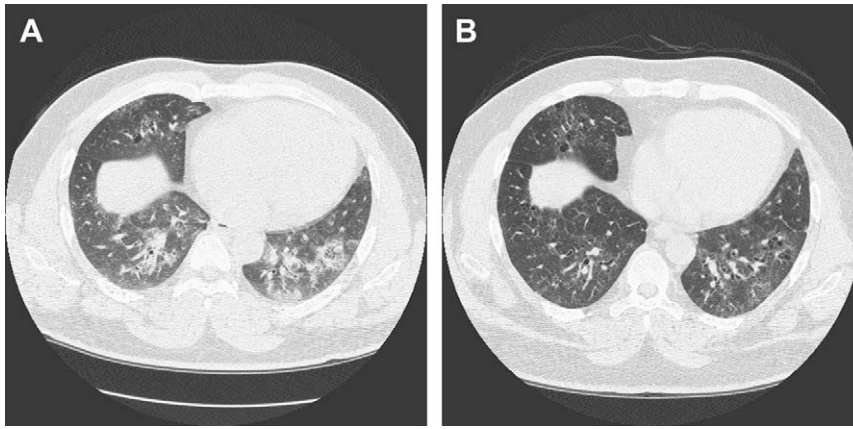

Fig. 2. (*A*) A high-resolution chest CT in expiration showing patchy bilateral ground glass airspace opacification on a background of more chronic changes. Patient had no sicca complaints but had Ro antibody and positive glandular scintigraphy. (*B*) Same patient. A high-resolution chest CT with lung windows. There are extensive fibrotic changes predominantly at the lung bases showing interstitial thickening, mild traction bronchiectasis, and some bullous changes in the right middle lobe.

ground glass changes, and parenchymal cysts, whereas micronodules were found more frequently in the upper zones. In 8% of the patients studied, honeycombing with architectural disruption consistent with pulmonary fibrosis was found, a figure that is consistent with previous reports.[50] In three of Uffman's patients, thin walled cysts were found, a comparatively rare pathology on Sjögren's patients, that has been reported by others[86,87] and sometimes is associated with pulmonary amyloidosis.

In the same journal, Koyama and colleagues[88] studied 60 consecutive patients who had primary SS and who fulfilled the criteria proposed by Fox and colleagues.[89] Fifty-three of these patients had never smoked. A predominance of lower zone pathology also was found, but a surprising number of patients (92%) had evidence of ground glass attenuation. Ten patients underwent histologic examination, and seven were found to have lymphocytic interstitial pneumonia. Two had NSIP, and one had bronchiolitis obliterans organizing pneumonia (BOOP).[88]

These studies have resulted in the conclusion that bronchiolar inflammatory changes and ILD are quite common abnormalities found on CT examination in patients who have SS (**Figs. 1** and **2**) and that high-resolution CT perhaps should be used as a screening test to detect abnormalities in these patients before functional abnormalities become evident.

Pulmonary Functional Tests

Vitali and colleagues determined that the most common abnormalities of pulmonary function in patients who have SS were tests indicative of small airway disease. Forced expiratory flow between 75% and 85% of forced vital capacity (FEF 75–85) and maximum expiratory flow at 75% of forced vital capacity (MEF 75) were abnormal, Abnormal diffusion capacity, coefficient of transfer of carbon monoxide (KCO) and diffusion capacity of carbon monoxide at the steady state (DLCOSS2) also were found to be abnormal. Fifty-five percent of patients with primary SS had abnormalities of MEF 75, KCO, and DLCO-SS.[34] These authors also confirmed that patients with secondary disease had more severe involvement.[34] Previous studies also had demonstrated significant abnormalities of diffusion[90,91] and obstructive defects.[92,93]

In a study comparing 61 patients who had primary SS with age- and sex- matched controls, it was determined that forced expiratory volume in 1 second (FEV1), MEF50, and MEF25 were all significantly different in patients compared with controls, whereas no significant difference was found in tests for carbon monoxide diffusion. These findings led the authors to conclude that small airway disease is the most common pulmonary manifestation found in patients who have and that it is frequently subclinical.[39] A 10-year follow-up study of 30 patients who had primary SS produced encouraging results.[37] These authors determined that patients who had Ro antibodies were more likely to develop pulmonary complaints and that pulmonary disease is an early manifestation of SS. Compared with the data obtained at 4 years of follow-up by the same authors,[94] the 10-year follow-up data demonstrated significant improvements in carbon monoxide transfer factor (TLco) and transfer coefficient (Kco) in some patients, suggesting that most patients do not develop progressive disease.[37] This study confirmed previous findings reported by Linstow and colleagues,[95] which also showed that TLco and Kco increased significantly in their patients after a period of 7 years follow-up.

Pathologic Tests

Bronchiolar lavage specimens may not be particularly helpful in evaluating pulmonary disease, although Shimizu and colleagues[96] suggested that the Th1/Th2 ratio of CD4 cells found on bronchiolar lavage, in patients with active interstitial pneumonia, may

help to distinguish between idiopathic pulmonary fibrosis and a connective tissue disease as the associated pathology. These authors demonstrated a dominance of Th1 cells found in patients who had a connective tissue disease and a dominance of Th2 cells found in patients who had idiopathic pulmonary fibrosis.[96] Dalavanga and colleagues[97] studied bronchiolar lavage specimens in 23 patients who had primary SS and compared them with controls. These authors determined that primary SS patients had a higher cell count in their bronchiolar lavage, with a greater percentage of lymphocytes when compared with controls. Those with the highest percentage of lymphocytes had more pulmonary complaints and radiographic evidence of interstitial disease.[98]

In most cases of pulmonary disease occurring in patients who have SS, however, a tissue biopsy, either open or closed, must be obtained, as the differential diagnosis in these patients is extensive (eg, rheumatoid nodules, sarcoidosis, lymphoma, and even amyloidosis). It should be remembered that even though sarcoidosis is an exclusionary criterion listed in the American European Consensus Criteria,[1] there have been several reports of SS and sarcoidosis coexisting in the same patient.[98,99]

SUMMARY

SS is a systemic disease with a predilection for the exocrine glands. It also is considered to be an autoimmune epitheliitis, and as the respiratory system is lined throughout with epithelial cells, it should not be surprising that patients who have SS may develop pulmonary disease. Pulmonary disease may be the initial presentation of SS in some patients,[25,26] and previous studies have suggested that patients presenting with idiopathic diffuse lung disease should be evaluated for an underlying connective tissue disease.[26,49] The typical pulmonary pathology found in patients who have SS reflects the basic inflammatory and lymphocytic aggressive nature of the disease. Pulmonary disease in patients who have primary SS may include dryness of the airways, hyper-reactive airway disease, ILD, lymphoproliferative diseases, pulmonary hypertension. and amyloidosis. Induction of BALT may result in lymphoid proliferation and invasion, leading to bronchial folliculitis, LIP, and pulmonary lymphoma. It is very likely that pulmonary pathology occurs more commonly than is appreciated, particularly as patients may be asymptomatic or present with mild complaints such as a nonproductive cough. It therefore should be routine practice for these patients to have regular chest radiographs and pulmonary function tests, especially if they have the type 1 phenotype of a low C4, palpable purpura, elevated IgM, and recurrent glandular swelling,[73] or they have Ro antibody and other extraglandular manifestations, including Raynaud's phenomenon.[34,37]

REFERENCES

1. Vital C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American–European Consensus Group. Ann Rheum Dis 2002;61:554–8.
2. Sjögren H. Zur Kenntnis de Keraconjunctivitis sicca (Keratitis filiformis bei Hypofunction der Tranendrusen). Acta Ophthalmol 1933;2:1–151.
3. Bloch KJ, Buchanan WW, Wohl MJ, et al. Sjögren's syndrome: a clinical pathological and serological study of 62 cases. Medicine (Baltimore) 1965;44:187–231.
4. Whaley K, Webb J, McAvoy BA, et al. Sjögren's syndrome, II: clinical associations and immunological phenomena. Q J Med 1973;42:513–48.
5. Manthorpe R, Asmussen K, Oxholm P. Primary Sjögren's syndrome: diagnostic criteria, clinical features, and disease activity. VIth International Symposium on

Sjögren's syndrome: Avon Connecticut, USA. J Rheumatol 1997;24(Suppl 50): 8–11.
6. Strand V, Talal N. Advances in the diagnosis and concept Sjögren's syndrome (autoimmune exocrinopathy). Bull Rheum Dis 1980;30(9):1046–52.
7. Moutsopoulos HM. Sjögren's syndrome autoimmune epithelitis. Clin Immunol Immunopathol 1994;72:162–5.
8. Fox R. Current approaches to managing inflammatory manifestations of Sjögren's syndrome. Medscape Rheumatology 2007;554326.
9. Mitsias DI, Kapsogeorgou ED, Moutsopoulos HM. The role of epithelial cells in the initiation and perpetuation of autoimmune lesions: lessons from Sjögren's syndrome (autoimmune epithelitis). Lupus 2006;15(5):255–61.
10. Kapsogeorgou EK, Dimitriou ID, Abu-Helu RF, et al. Activation of epithelial and myoepithelial cells in the salivary glands of patients with Sjögren's syndrome: high expression of intercellular adhesion molecule-1 (ICAM.1) in biopsy specimens and cultured cells. Clin Exp Immunol 2001;124:126–33.
11. Lindahl G, Hedfors E, Klareskog L, et al. Epithelial HLA-DR expression and T lymphocyte subsets in salivary glands in Sjögren's syndrome. Clin Exp Immunol 1985;61:475–82.
12. Fox RI, Bumol T, Fantozzi R, et al. Expression of histocompatibility antigen HLA-DR by salivary gland epithelial cells in Sjögren's syndrome. Arthritis Rheum 1986;29:105–11.
13. Manoussakis MN, Dimitriou ID, Kapsogeorgou EK, et al. Expression of B7 costimulatory molecules by salivary gland epithelial cells in patients with Sjögren's syndrome. Arthritis Rheum 1999;42:229–39.
14. Boumba D, Skopouli FN, Moutsopoulos HM. Cytokine mRNA expression in the labial salivary gland tissues from patients with primary Sjögren's syndrome. Br J Rheumatol 1995;34:326–33.
15. Xanthou G, Polihronis M, Tzioufas AG, et al. Lymphoid chemokine messenger RNA expressions by epithelial cells in the chronic inflammatory lesion of the salivary glands of Sjögren's syndrome patients: possible participation in lymphoid structure formation. Arthritis Rheum 2001;44:408–18.
16. Chisholm DM, Mason DK. Labial salivary gland biopsy in Sjögren's syndrome. J Clin Pathol 1968;21:656–60.
17. Sumida T, Yonaha F, Maedia T, et al. Expression of sequences homologous to HTLV-1 Tax gene in the labial salivary glands of Japanese patients with Sjögren's syndrome. Arthritis Rheum 1994;37:545–50.
18. Cannon MJ, Pisa P, Fox RI, et al. Epstein-Barr virus induces aggressive lymphoproliferative disorders of human B cell origin in SCID/bu chimeric mice. J Clin Invest 1990;85:1333–7.
19. Sutinen S, Sutinen S, Huhti E. Ultrastructure of lymphoid interstitial pneumonia: virus-like particles in bronchiolar epithelium of a patient with Sjögren's syndrome. Am J Clin Pathol 1977;67:328–33.
20. Triantafyllopoulou A, Tapinos N, Moutsopoulos HM. Evidence for coxsackievirus infection in primary Sjögren's syndrome. Arthritis Rheum 2004;50:2897–902.
21. Itescu S, Brancato LJ, Winchester R. A sicca syndrome in HIV infection: association with HLA-DR5 and CD8 lymphocytes. Lancet 1989;334(ii):466–8.
22. Itescu S. Diffuse infiltrative lymphocytosis syndrome in human immunodeficiency virus infection—a Sjögren's-like disease. Rheum Dis Clin North Am 1991;vol. 17(1):99–115.
23. Coll J, Gambus G, Corominas J, et al. Immunohistochemistry of minor salivary gland biopsy specimens from patients with Sjögren's syndrome with and without hepatitis C virus infection. Ann Rheum Dis 1997;56(6):390–2.

24. Ramos-Casals M, Garcia-Carrusco M, Brio Zeron MP, et al. Viral etiopathogenesis of Sjögren's syndrome: role of hepatitis C virus. Autoimmun Rev 2002;1:238–43.
25. Reuss-Borst MA, Hartmann U. Pulmonary nodules as initial manifestation of primary Sjögren's syndrome. Ann Rheum Dis 2006;65(5):685–7.
26. Kurumagawa T, Kobayashi H, Motoyoshi K. Potential involvement of subclinical Sjögren's syndrome in various lung diseases. Respirology 2005;10(1):86–91.
27. Adamson TC III, Fox RI, Frisman DM, et al. Immunohistologic analysis of lymphoid infiltrates in primary Sjögren's syndrome using monoclonal antibodies. J Immunol 1983;130:203–8.
28. Xanthou G, Tapinos NI, Polihronis M, et al. CD4 cytotoxic and dendritic cells in the immunopathologic lesion of Sjögren's syndrome. Clin Exp Immunol 1999;118: 154–63.
29. Tala N, Bunim JJ. The development of malignant lymphoma in the course of Sjögren's syndrome. Am J Med 1964;36:529–40.
30. Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. Ann Intern Med 1978;89:888–92.
31. Voulgarelis M, Dafni UG, Isenberg DA, et al. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European concerted action on Sjögren's syndrome. Arthritis Rheum 1999;42:1765–72.
32. Constantopoulos SH, Papadimitriou CS, Moutsopoulos HM. Respiratory manifestations in primary Sjögren's syndrome. A clinical functional and histologic study. Chest 1985;88:226–9.
33. Papathanasiou MP, Constaniopoulos SH, Tsampoulas C, et al. Reappraisal of respiratory abnormalities in primary and secondary Sjögren's syndrome. A controlled study. Chest 1896;90:370–4.
34. Vitali C, Tavoni A, Viegi G, et al. Lung involvement in Sjögren's syndrome: a comparison between patients with primary and with secondary syndrome. Ann Rheum Dis 1985;44:455–61.
35. Leslie KO, Trahan S, Gruden J. Pulmonary pathology of the rheumatic diseases. Semin Respir Crit Care Med 2007;28(4):369–78.
36. Hansen LA, Prakash UB, Colby TV. Pulmonary lymphoma in Sjögren's syndrome. Mayo Clin Proc 1989;64:920–31.
37. Davidson BK, Kelly CA, Griffiths ID. Ten-year follow-up of pulmonary function in patients with primary Sjögren's syndrome. Ann Rheum Dis 2000;59:709–12.
38. Constantopoulos SH, Drosos AA, Maddison PI, et al. Xerotrachea and interstitial lung disease in primary Sjögren's syndrome. Respiration 1984;46:310–4.
39. Lahdensuo A, Korpela M. Pulmonary findings in patients with primary Sjögren's syndrome. Chest 1995;108:316–9.
40. Ellman P, Parkes Weber F. Sjögren's disease with dryness of the bronchial mucosa and uncertain lung lesion. BMJ 1949;1:304–5.
41. Papiris SA, Maniati M, Constantopoulos SH, et al. Lung involvement in primary Sjögren's syndrome is mainly related to the small airway disease. Ann Rheum Dis 1999;58:61–4.
42. Andoh Y, Shimura S, Sawai T, et al. Morphometric analysis of airways in Sjögren's syndrome. Am Rev Respir Dis 1993;148:1358–62.
43. Papiris SA, Saetta M, Turato G, et al. CD4-positive T lymphocytes infiltrate the bronchial mucosa of patients with Sjögren's syndrome. Am J Respir Crit Care Med 1997;156:637–41.
44. Dalavanga YA, Voulgari PV, Georgiadis AN, et al. Lymphocytic alveolitis: a surprising index of poor prognosis in patients with primary Sjögren's syndrome. Rheumatol Int 2006;26:799–804.

45. Sakamoto O, Saita N, Ando M, et al. Two cases of Sjögren's syndrome with multiple bullae. Intern Med 2002;41:124–8.
46. Hubscher O, Re R, Iotti R. Cystic lung disease in Sjögren's syndrome. J Rheumatol 2002;29:2235–6.
47. Tokuyasu H, Watanabe E, Okazaki R, et al. Sjögren's syndrome with multiple bullae caused by lymphocytic interstitial pneumonia. Lung 2007;185(3):187–8.
48. Tzelepis GE, Toya SP, Moutsopoulos HM. Occult connective tissue diseases mimicking idiopathic interstitial pneumonias. Eur Respir J 2008;31:11–20.
49. Strange C, Highland KB. Interstitial lung disease in the patient who has connective tissue disease. Clin Chest Med 2004;25:549–59, viii.
50. Gardiner P, Ward C, Allison A, et al. Pleuropulmonary abnormalities in primary Sjögren's syndrome. J Rheumatol 1993;20:831–7.
51. Parambil JG, Myers JL, Lindell RM, et al. Interstitial lung disease in primary Sjögren's syndrome. Chest 2006;130:1489–95.
52. Tansey D, Wells AU, Colby TV, et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004;44:585–96.
53. Fujita J, Ohtsuki Y, Yoshinouchi T, et al. Idiopathic nonspecific interstitial pneumonia: as an autoimmune interstitial pneumonia. Respir Med 2005;99:234–40.
54. Nakamura Y, Chida K, Suda T, et al. Nonspecific interstitial pneumonia in collagen vascular diseases: comparison of the clinical characteristics and prognostic significance with usual interstitial pneumonia, sarcoidosis, vasculitis. Sarcoidosis Vasc Diffuse Lung Dis 2003;20:235–41.
55. Ito I, Nagai S, Kitaichi M, et al. Pulmonary manifestations of primary Sjögren's syndrome: a clinical radiologic, and pathologic study. Am J Respir Crit Care Med 2005;171:632–8.
56. Swigris JJ, Berry GJ, Raffin TA, et al. Lymphoid interstitial pneumonia. Chest 2002;122:2150–64.
57. Strimlan CV, Rosenow EC, Weiland L, et al. Lymphocytic interstitial pneumonitis: review of 13 cases. Ann Intern Med 1978;88:616–21.
58. Koss M, Hochholzer L, Langloss J, et al. Lymphoid interstitial pneumonia: linicopathological and immunopathologic findings in 18 cases. Pathology 1987;19:178–85.
59. Centers for Disease Control. Classification system for HIV infection in children under 13 years of age. MMWR Morb Mortal Wkly Rep 1987;36:225–30.
60. Itescu S, Brancato LJ, Buxbaum J, et al. A diffuse infiltrative CD8 lymphocytosis syndrome in human immunodeficiency virus (HIV) infection; a host immune response associated with HLA-DR5. Ann Intern Med 1990;112:3–10.
61. Kazi S, Cohen P, Williams F, et al. The diffuse infiltrative lymphocyte syndrome: clinical and immunogenetic features in 35 patients. AIDS 1996;10:385–91.
62. Williams F, Cohen P, Jumshyd J, et al. Prevalence of the diffuse infiltrative lymphocytosis syndrome among human immunodeficiency virus type I-positive outpatients. Arthritis Rheum 1998;41:863–8.
63. American Thoracic Society/European Respiratory Society. International Multidisciplinary Consensus Classification of Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee 2001. Am J Respir Crit Care Med 2002;165:277–304.
64. Agusti C, Xaubet A, Roca J, et al. Interstitial pulmonary fibrosis with and without associated collagen vascular disease: results of a two-year follow-up. Thorax 1992;47:1035–40.

65. Wells AU, Cullinan P, Hansell DM, et al. Fibrosing alveolitis is associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1994;149:1583–90.
66. Flaherty KR, Colby TV, Travis WD, et al. Fibroblastic foci in usual interstitial pneumonia: idiopathic versus collagen vascular disease. Am J Respir Crit Care Med 2003;167:1410–5.
67. Park JH, Kim DS, Park IN, et al. Prognosis of fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2007;175:705–11.
68. Anderson LG, Talal N. The spectrum of benign to malignant lymphoproliferation in Sjögren's syndrome. Clin Exp Immunol 1972;10:199–221.
69. Mariette X. Lymphoma in patients with Sjögren's syndrome: review of the literature and physiopathologic hypothesis. Leuk lymphoma 1999;33:93–9.
70. Royer B, Cazals-Hatem D, Sibilia J, et al. Lymphomas in patients with Sjögren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. Blood 1997;90:766–75.
71. Theander E, Manthorpe R, Jacobsson LTH. Mortality and causes of death in primary Sjögren's syndrome: a prospective cohort study. Arthritis Rheum 2004; 50(4):1262–9.
72. Ioannidis JP, Vassiliou VA, Mountsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum 2002;46:741–7.
73. Sminia T, van der Brugge-Gamelkoorn GJ, Jeurissen SHM. Structure and function of bronchus- associated lymphoid tissues (BALT). Crit Rev Immunol 1989;9: 119–50.
74. Pabst R. Is BALT a major component of the human lung immune system? Immunol Today 1992;13:119–22.
75. Korst RJ. Primary lymphoma of the subglottic airway in a patient with Sjögren's syndrome mimicking high laryngotracheal stenosis. Ann Thorac Surg 2007; 84(5):1756–8.
76. Kurtin PJ, Myers JL, Adlakha H, et al. Pathologic and clinical features of primary pulmonary extranodal marginal zone B-cell lymphoma of MALT type. Am J Surg Pathol 2001;25:997–1008.
77. Begueret H, Vergier B, Parrens M, et al. Primary lung small B-cell lymphoma versus lymphoid hyperplasic. Am J Surg Pathol 2002;26:76–81.
78. Papiris SA, Kalomenidis I, Malagari K, et al. Extranodal marginal zone B-cell lymphoma of the lung in Sjögren's syndrome patients: reappraisal of clinical, radiological, and pathology findings. Respir Med 2007;101(1):84–92.
79. Bertoni M, Niccoli L, Porciello G, et al. Pulmonary hypertension in primary Sjögren's syndrome: report of a case and review the literature. Clin Rheumatol 2005;24(4):431–4.
80. Launay D, Hachull AE, Hatron PY, et al. Pulmonary arterial hypertension: a rare complication of primary Sjögren's syndrome: report of 9 new cases and review of the literature. Medicine (Baltimore) 2007;86(5):299–315.
81. Chen CH, Chen HA, Yang KY, et al. Clinical features and endothelia receptor antagonist in primary Sjögren's syndrome with pulmonary arterial hypertension. Scand J Rheumatol 2006;35(3):245–7.
82. Niepolski L, Grzegorzewska AE, Szymas J. Nodular pulmonary amyloidosis and Sjögren's syndrome in a patient treated with intermittent haemodialysis(IHD). Nephrol Dial Transplant 2007;22(5):1485–6.
83. Sugai S. Mucosa-associated lymphoid tissue (MALT) lymphoma and primary amyloidosis in the lung in Sjögren's syndrome. Intern Med 2002;41:251–2.

84. Uffman M, Kiener HP, Bankier AA, et al. Lung manifestation in asymptomatic patients with primary Sjögren's syndrome: assessment with high-resolution CT and pulmonary function tests. J Thorac Imaging 2001;16(4):282–9.
85. Franquet T, Gimenez A, Mondl JM, et al. Sjögren's syndrome and associated lung disease CT findings in 50 patients. AJR Am J Roentgenol 1997;169:655–8.
86. Meyer CA, Pina JS, Taillon D, et al. Inspiratory and expiratory high-resolution CT findings in a patient with Sjögren's syndrome and cystic lung disease. AJR Am J Roentgenol 1997;168:101–3.
87. Inase N, Usui Y, Tachi H, et al. Sjögren's syndrome and bronchial gland involvement and multiple bullae. Respiration 1990;57:286–8.
88. Koyama M, Johkoh T, Honda O, et al. Pulmonary involvement in primary Sjögren's syndrome: spectrum of pulmonary abnormalities and computed tomography findings in 60 patients. J Thorac Imaging 2001;16(4):290–6.
89. Fox RI, Saito J. Criteria for diagnosis of Sjögren's syndrome. Rheum Dis Clin North Am 1974;20:391–407.
90. Strimlan CV, Rosenow EC III, Divertie MB, et al. Pulmonary manifestations of Sjögren's syndrome. Chest 1976;70:354–61.
91. Oxholm P, Bundgaard A, Birk Madsen E, et al. Pulmonary function in patients with primary Sjögren's syndrome. Rheumatol Int 1982;2:179–81.
92. Newball HH, Brahim SA. Chronic obstructive airway disease in patients with Sjögren's syndrome. Am Rev Respir Dis 1977;115:295–304.
93. Segal I, Fink G, Machtey I, et al. Pulmonary function abnormalities in Sjögren's syndrome and the sicca complex. Thorax 1981;36:286–9.
94. Kelly C, Gardiner P, Pal B, et al. Lung function in primary Sjögren's syndrome: a cross- sectional and longitudinal study. Thorax 1991;46:180–3.
95. Linstow M, Kriegbaum NJ, Backer V, et al. A follow-up study of pulmonary function in patients with primary Sjögren's syndrome. Rheumatol Int 1990;10:47–9.
96. Shimizu Y, Kuwabara H, Ono A, et al. Intracellular Th1/Th2 balance of pulmonary CD4(+) T cells in patients with active interstitial pneumonia evaluated by serum KL-6. Immunopharmacol Immunotoxicol 2006;28(2):295–304.
97. Dalavanga YA, Constantopoulos SH, Galanopoulou V, et al. Alveolitis correlates with clinical pulmonary involvement in primary Sjögren's syndrome. Chest 1991;99:1394–7.
98. Gal I, Kovacs J, Zeher M. Case series: coexistence of Sjögren's syndrome and sarcoidosis. J Rheumatol 2000;27:2507–10.
99. Ramos-Casals M, Brito-Zeron P, Garcia-Carrasco M, et al. Sarcoidosis or Sjögren's syndrome? Clues to defining mimicry or coexistence in 59 cases. Medicine 2004;83(2):85–95.

Mucosa-Associated Lymphoid Tissue Lymphoma in Sjögren's Syndrome: Risks, Management, and Prognosis

Michael Voulgarelis, MD*, Haralampos M. Moutsopoulos, MD, FACP, FRCP

KEYWORDS

- Sjögren's syndrome • Lymphoma • Lymphoproliferation
- Predictive factors • MALT • Autoimmunity
- Marginal zone B-cell lymphoma

Over the years, several studies have linked certain autoimmune and chronic inflammatory conditions, including rheumatoid arthritis, Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), celiac disease, and chronic thyroiditis to an increased occurrence of lymphoma.[1] The relationship between SS and lymphoma has been known since 1963.[2] Kassan and colleagues[3] later reported that patients who have SS have a 44 times greater relative risk of lymphoma development than age-matched women in the general population. Several reports subsequently supported the association of lymphoma with SS and recognized non-Hodgkin's lymphoma (NHL) as a major complication in the progression of the disease.[4–10] In addition, patients who have primary SS are more susceptible to developing lymphoma than patients who have other autoimmune diseases such as SLE and rheumatoid arthritis. A recent meta-analysis estimated the risk of lymphoma development in autoimmune diseases such as SS, SLE, and rheumatoid arthritis, showing a high risk for SS (random effects standardized incidence rate [SIR] = 18.9; 95% confidence interval [CI], 9.4–37.9), a moderate risk for SLE (random effects SIR = 7.52; 95% CI, 3.3–17.3), and a lower risk for rheumatoid arthritis (random effects SIR = 3.25; 95% CI, 2.05–5.16) (**Fig. 1**).[11]

SS is otherwise a benign autoimmune disease with slow progression and low morbidity and mortality, characterized by broad organ-specific and systemic

Department of Pathophysiology, Medical School, National University of Athens, 75 Mikras Asias Street, 11527 Athens, Greece
* Corresponding author.
E-mail address: mvoulgar@med.uoa.gr (M. Voulgarelis).

Rheum Dis Clin N Am 34 (2008) 921–933
doi:10.1016/j.rdc.2008.08.006 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

Fig. 1. Lymphoma in autoimmune disorders. The association between autoimmune diseases and lymphomas is well established. The authors' department recently reviewed data from 20 studies that evaluated individuals who had autoimmune diseases and their incidence of lymphoma development. The data included individuals who had rheumatoid arthritis (RA), Sjögren's syndrome (SS), or systemic lupus erythematous (SLE). Individuals who had any autoimmune disorder had a greater risk of developing NHL than the general population; however, this risk varied among the diseases. Individuals who had SS had a higher risk for developing NHL. *(Data from* Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med 2005;165:2337–44.)

manifestations, the most common being diminished lacrimal and salivary gland function, xerostomia, keratoconjunctivitis, and parotid gland enlargement. What makes the syndrome particularly interesting is that this benign autoimmune process potentially can lead to malignant NHL, rendering it an ideal model for the study of human lymphoma development. The transition to malignant lymphoproliferation affects only a subgroup of patients who have SS and is characterized by the appearance of certain clinical and serologic parameters early in the natural course of disease.[3–5] The recognition of these predictive markers is crucial for clinical monitoring and potential therapeutic intervention.

MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA IN SJÖGREN'S SYNDROME: CLINICAL ASPECTS AND HISTOPATHOLOGY

NHL has a 4.3% prevalence in patients who have SS. In these patients the median age at lymphoma diagnosis is 58 years, and the median time from SS diagnosis to lymphoma diagnosis is 7.5 years.[3,12] Various histologic subtypes of NHL occurring in patients who have SS have been described in the literature, including follicle center lymphoma, lymphoplasmacytoid lymphoma, and diffuse large B-cell lymphoma (DLBCL), but mucosa-associated lymphoid tissue (MALT) lymphomas are by far the most common.[3–14] In a series of 33 cases of parotid MALT lymphoma, almost half the patients had a history of SS.[15] A recent case-control study showed both a 28-fold increased risk of marginal zone (MZ) B-cell lymphoma (including MALT lymphomas) and an 11-fold increased risk of DLBCL in patients who had SS.[16]

In general, extranodal MZ B-cell lymphoma of MALT type is the third commonest NHL, and its incidence has risen steadily during the last 2 decades.[17,18] MALT lymphoma is an indolent disease frequently located in both mucosal and nonmucosal extranodal sites, most of which have in common the presence of epithelium, suggesting that these cells home close to epithelia rather than mucosa.[19,20] The majority of the organs in which MALT lymphomas develop are devoid of lymphoid tissue, and in most

cases MALT acquisition precedes lymphoma development. Although these lymphomas are associated with several infectious agents or autoimmune disorders such as SS or Hashimoto thyroiditis, they all seem to derive from neoplastic transformation of MZ B lymphocytes.[13]

Although MALT lymphomas arise at different anatomic sites, they nevertheless share common morphologic features.[21] The histologic features of MALT lymphoma closely resemble those of Peyer's patch lymphoid tissue. More specifically, the histopathology includes (1) reactive lymphoid follicles, with or without colonization by neoplastic cells; (2) MZ (centrocyte-like cells) and/or monocytoid B cells that infiltrate the overlying epithelium (lymphoepithelial lesions); (3) small B lymphocytes; (4) and plasma cells (which may or may not be neoplastic).[22] The presence of lymphoepithelial lesions is an important diagnostic feature, defined by the infiltration and distortion of epithelial structures by aggregates of neoplastic lymphoid cells. The first morphologic manifestation of MALT lymphoma in SS is the presence of haloes of pale monocytoid B cells around the epimyoepithelial islands.[23] Such infiltrates show immunoglobulin light-chain restriction, and a clonal B-cell population can be demonstrated by polymerase chain reaction.[24] More established MALT lymphomas are characterized by extensive proliferation of neoplastic cells, gradual replacement of reactive follicles, and dilatations of ducts. The immunophenotype of MALT lymphoma cells recapitulates that of the MZ B cell. Typically, tumors express pan-B antigen (CD19, CD20, CD22, CD79a) but do not express CD5, CD10, CD23, or Bcl-1 (**Fig. 2**).

MZ lymphomas of MALT type in patients who have SS usually are low grade and localized (stage I and II) with extranodal manifestations.[12] The clinical presentation varies according to the lymphoma location, but certain characteristics are common. The main features include a small tumor burden, excellent performance status, and normal lactate dehydrogenase (LDH) and β2-microglobulin levels (**Table 1**).[12] The salivary glands are the most commonly affected site, but other extranodal sites such as the stomach, nasopharynx, skin, liver, kidney, and lung also can be involved. Twenty percent of the patients displayed involvement of more than one extranodal site at diagnosis, indicating that these lymphomas preferentially migrate to other mucosal sites, thereby emphasizing the need for complete staging procedures in patients who have SS and MALT lymphomas. The lymphoma rarely involves peripheral lymph nodes but frequently disseminates to loco-regional lymph nodes. Nodal presentation can represent either a nodal spread of a primary extranodal MZ lymphoma or the less common nodal (monocytoid) MZ lymphoma.

Major gland enlargement, mainly bilateral parotid gland enlargement, is the main presenting sign. The clinical picture in these patients is characterized by the absence of B symptoms; although more than one extranodal site can be involved in disseminated disease, bone marrow infiltration is rare (10%). Skin vasculitis and peripheral nerve involvement are frequent manifestations, in contrast to other MALT lymphomas in the non-SS population. Renal involvement, anemia, lymphopenia, monoclonal immunoglobulins, and mixed monoclonal cryoglobulinemia (MMC) also are particularly common in SS-related MALT lymphoma. The presence of salivary gland enlargement, lymphadenopathy, splenomegaly, skin vasculitis, and peripheral neuropathy should alert the physician to the presence of NHL.

Lymphomas in patients who have SS tend to evolve toward a less-differentiated cell type in 10% of cases.[12] Histologically, the transformation of MALT lymphoma to DLBCL is heralded by the emergence of an increased number of transformed blasts forming sheets or clusters that ultimately efface the preceding MALT lymphoma. Most high-grade lymphomas located in salivary glands are DLBCLs. Precisely what percentage of DLBCLs arises from pre-existing MALT or follicular lymphoma is unknown.

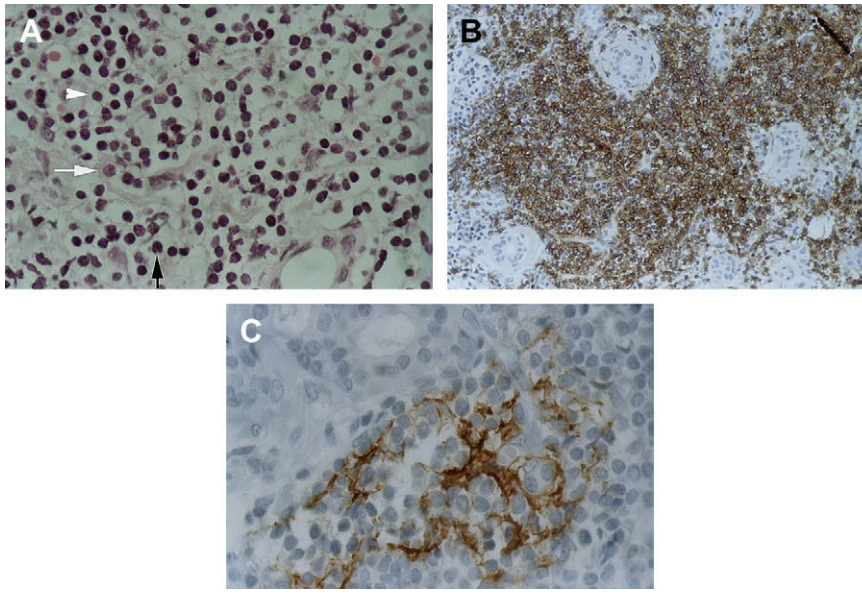

Fig. 2. Salivary MALT type lymphoma. (*A*) The lymphoid infiltrate is composed of small lymphocytes, centrocyte-like B cells (*black arrow*), and monocytoid B cells (*white arrowhead*) as well as plasma cells (*white arrow*) (hematoxylin and eosin, original magnification × 200). (*B*) Atypical lymphoid cells diffusely positive for CD20 (immunostaining with L26 antibody, original magnification × 100). In addition, there were about four times more lambda light-chain–positive plasma cells than kappa light-chain–positive cells. (*C*) Staining (anti-CD21, original magnification × 200) for follicular dendritic cells (FDCs) reveals overrun follicles by showing the residual meshwork of FDCs indicative of follicular colonization. These results, together with the histologic findings, confirmed that the lesion was a B-cell lymphoma, compatible with low-grade lymphoma of the MALT type.

Immunohistochemical, karyotypic, and genotypic studies have provided convincing proof that the supervening large-cell lymphomas arise from the same clone as the low-grade lymphomas. Thus most high-grade lymphomas in patients who have SS may represent blastic variants of either MZ B-cell or follicular center-cell lymphomas.[25] Genetic alterations that have been implicated in the histologic transformation of MALT lymphomas include *p53* allelic loss and mutation, hypermethylation of *p15* and *p16* genes, and *p16* gene deletions.[26,27] Transformation is characterized clinically by further nodal and extranodal dissemination.[12] Although disseminated MALT lymphomas in patients who have SS carry a good prognosis, the histologic transformation to a high-grade lymphoma always signifies a poor outcome.[12,28] Therefore, the identification of de novo or secondary DLBCLs in patients who have SS is crucial to prognosis, because in both cases the median overall survival has been estimated to be only 1.8 years.[12]

CLINICAL AND SEROLOGIC RISK FACTORS OF LYMPHOMA DEVELOPMENT IN SJÖGREN'S SYNDROME

Despite its unequivocal association with SS, the development of lymphoma constitutes a complication rather than the rule. Only 5% of patients who have SS ultimately manifest lymphoma. Several investigations have attempted to establish predictive markers for this progression. In 1971 Anderson and Talal[29] showed that a decrease

Table 1
Clinical characteristics of patients who have Sjögren's syndrome and who have low-grade extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue type

Clinical Characteristic	% Positive
Performance status (grade 0–1)	85
B symptoms[a]	15
Clinical stage (localized disease)	61
Involvement	
Nodal	15
Extranodal	46
Both	39
Splenomegaly	7
Bone marrow infiltration	7
Bulky disease	7
Low-risk group according to International Prognostic Index (IPI)[b]	68

[a] B symptoms are fever (ie, temperature > 38°C), weight loss exceeding 10% of body weight in 6 months, and drenching night sweats.
[b] The International Prognostic Index (IPI) was designed to clarify lymphoma staging. The IPI predicts the risk of disease recurrence and overall survival by taking into account factors such as age (< 60 years versus > 60 years), stage of disease (stage I or II versus stage III or IV), general health (also known as performance status, grade 0 or 1 versus grade 2–4), number of extranodal sites (0 or 1 versus 2–4), and the presence or absence of an elevated LDH level. Patients who have two or more risk factors have a less than 50% chance of relapse-free and overall survival at 5 years.

in the level of serum immunoglobulins and disappearance of rheumatoid factor coincided with the time of progression to lymphoma. Kassan and colleagues[3] showed that patients who have lymphadenopathy, splenomegaly, parotid gland enlargement, and a history of low-dose irradiation or chemotherapy have an increased risk of developing lymphoma. The authors' department found the presence of MMC to be the most significant factor in predicting the risk of lymphoma development.[30] Others have suggested that monoclonal paraproteinemia and urinary free light chains could signify a particular risk of subsequent development of lymphoma.[31] In an attempt to identify simple but reliable clinical and serologic markers of an increased risk for lymphoproliferation, the authors examined a large cohort and concluded that lymphoma development is associated with the presence of palpable purpura, low C4 levels, and MMC.[32] Ioannidis and colleagues[33] confirmed that lymphoproliferative disease is predicted independently by parotid gland enlargement, palpable purpura, and low C4 levels. In the absence of these factors, the risk of lymphoma development is negligible. Notably, Ramos-Casals and colleagues[34] demonstrated that lymphoma was associated with low C3, C4, and CH50 levels in univariate analysis, although in multivariate analysis only low C4 levels alone proved to be independent significant variable. Others have suggested that leg ulcers, manifesting as vasculitis, as well as CD4+ T-lymphocytopenia, are predictive of lymphoma development.[10,35] Finally, high serum β-2 microglobulin levels, low serum IgM levels, and the disappearance of a previously positive rheumatoid factor are other biologic predictors of NHL development in patients who have SS.[36] Specific associations between immunosuppressive treatment and lymphoma risk in patients who have SS have been reported rarely.[1] These data suggest that although some clinical parameters may herald the imminent onset of lymphoma, few reliable markers are available to predict this progression (**Box 1**).

Box 1
Clinical and serologic predictors of lymphoma development in Sjögren's syndrome

- Splenomegaly
- Persistent enlargement of parotid glands
- Serum or urine monoclonal bands
- Lymphadenopathy
- Palpable purpura
- Leg ulcers
- Peripheral neuropathy
- Low levels of C4
- High serum β2-microglobulin
- CD4 lymphocytopenia
- Mixed monoclonal cryoglobulinemia

Patients who have these risk factors constitute a separate subgroup that should be monitored and managed more closely than other patients who have SS.

MANAGEMENT OF MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMAS ASSOCIATED WITH SJÖGREN'S SYNDROME

Large series have demonstrated that nongastric MALT lymphomas in patients who do not have SS seem to have a good outcome, with a 5-year overall survival rate from diagnosis ranging from 86% to 100%.[37,38] Although 30% of these patients presented with disseminated disease, their outcome remained unaffected by the multifocal nature of the lymphoma.[28] The finding that patients presenting with extranodal MALT lymphoma affecting multiple mucosal sites have a favorable outcome with survival curves similar to those of patients who have localized disease renders the use of the traditional Ann Arbor staging system problematic. The Ann Arbor staging system is based mainly on the number of involved areas, both nodal and extranodal, and thus can be misleading in the case of MALT lymphomas. Regardless of the presentation site, diagnostic studies always should include the standard lymphoma staging procedures and in addition the examination of Waldeyer's ring. Once the diagnosis of MALT lymphoma is established, a radiographic examination with CT scans of the neck, chest, abdomen, and pelvis should follow. Laboratory evaluation also should include a complete blood cell count, chemistry panel, MMC, LDH level, and serum protein electrophoresis. Furthermore, bone marrow aspiration and biopsy are necessary to assess possible dissemination to the marrow. The initial staging should include a gastroduodenal endoscopy with multiple blind biopsies as well as biopsies from any site that appears macroscopically abnormal. A possible *Helicobacter pylori* infection also needs to be excluded. Special diagnostic procedures may prove necessary. In this regard, pulmonary opacities should be assessed histologically for the exclusion of bronchial MALT lymphoma. An endoscopic ultrasound is strongly recommended in the case of gastric involvement (**Box 2**).

Despite the abundance of literature on the histopathologic and biologic features of MALT lymphomas, treatment data remain limited. Furthermore, none of the conventional oncologic approaches seem to influence the outcome of these patients.[28] It is

Box 2
Staging procedures for mucosa-associated lymphoid tissue lymphoma in Sjögren's syndrome

- History
- Physical examination
- CT scan of neck, thorax, and abdomen
- Laboratory tests (blood cell count, LDH level, serum electrophoresis and immunofixation, renal and liver tests, HIV and Hepatitis C virus serology, cryoglobulins, functional thyroid tests, and C4 and albumin levels)
- Bone marrow biopsy
- Depending on the symptoms at diagnosis
  - Gastric endoscopy and endoscopic ultrasound
  - Bronchoscopy plus lavage
  - Orbit MRI and ophthalmologic examination

important to remember that some patients who have persistent disease may be managed expectantly without active therapy and go on to have a normal lifespan. In one retrospective analysis, Ambrosetti and colleagues[15] reported no significant differences in outcomes among patients who had SS and salivary MALT lymphomas who had undergone a variety of treatment modalities, including surgery, radiotherapy, and chemotherapy, and those who had received no treatment at all. This finding is consistent with one of the authors' studies, which demonstrated that patients who have SS and indolent salivary MALT lymphomas usually have a quite uncomplicated clinical course with a median overall survival of 6.4 years. In this study, at a median follow-up of 6 years, overall survival rates were the same in patients who had treated and untreated MALT lymphomas.[12]

The histologic grade, a very important prognostic factor for overall survival, dictates the treatment of SS-associated NHL.[39] Thus, a policy of watchful waiting is recommended in patients who have localized low-grade MALT lymphoma affecting the exocrine glands. In this instance, very thorough staging procedures are mandatory. In contrast, when multiple extranodal sites are involved, treatment with single-agent chemotherapy is indicated. Alkylating agents (chlorambucil or cyclophosphamide), purine analogues, and the biologic agent rituximab seem to be equally suitable options, although this equivalence has yet to be substantiated by large series and randomized studies.[40–43] In patients who have disseminated disease at presentation, single agents such as alkylating agent or purine analogue have been reported to induce a 75% complete remission (CR) rate, with projected 5-year event-free and overall survival rates of 50% and 75%, respectively.[40] In a previous study, the authors reported a 75% CR rate with the purine analogue 2-chloro-2-deoxyadenosine (2-CdA) in patients who had SS-associated B-cell lymphoma during a 4-year follow-up. Notably, an improvement in some SS features was observed (ie, oral symptoms, parotidomegaly, salivary flows, hyposthenuria, and disappearance of cryo/urine monoclonal bands).[44] In addition to its direct cytotoxic potential, 2-CdA was associated with pronounced T-cell depletion. This depletion could explain the drug's efficacy in MALT lymphoma, given the potential implication of antigen-specific T cells in lymphomagenesis.[45] Rituximab also has been shown to be a viable therapeutic agent in the treatment of SS, both with or without associated MALT-type lymphoma, as indicated by an open-labeled phase II study.[46] A recent case report described CR of a MALT-type lymphoma of the parotid

gland following rituximab therapy as well as improvement in the histologic and sialometric characteristics of a patient who had SS.[47] The high relapse rate in patients who have MALT type MZ lymphomas warrants regular follow-up, however. Finally, doxorubicin-based combined chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP) should be reserved for patients who have a high tumor burden as indicated by a high LDH level, a tumor mass greater than 7 cm, and bulky regional nodal involvement (**Fig. 3**).[48]

During the last 15 years a number of aggressive induction regimens have been used to treat patients who have high-grade lymphomas. When these regimens subsequently were compared with the reference-standard regimen, CHOP, in large, randomized trials, however, the aggressive induction regiments showed no advantage in CR and overall survival. Consequently, most patients who have SS and aggressive NHL receive an anthracycline-containing regimen such as CHOP. Unfortunately, the median survival is estimated to be only 1.8 years in these patients. The presence of B symptoms and a large tumor diameter (> 7 cm) are additional independent factors indicating an increased risk of death.[12] This observation, together with data indicating that rituximab plus CHOP (R-CHOP) had a significant clinical effect in DLBCL, increasing both response rate and survival compared with CHOP alone, prompted the authors to use R-CHOP in six patients who had SS and aggressive NHL.[49,50] The study revealed that R-CHOP induced sustained CR in all patients who had SS and aggressive de novo or secondary DLBCL during a follow-up period of 2 years. Moreover, extranodal manifestations such as peripheral neuropathy and skin vasculitis disappeared after eight cycles of R-CHOP, a remission that was accompanied by

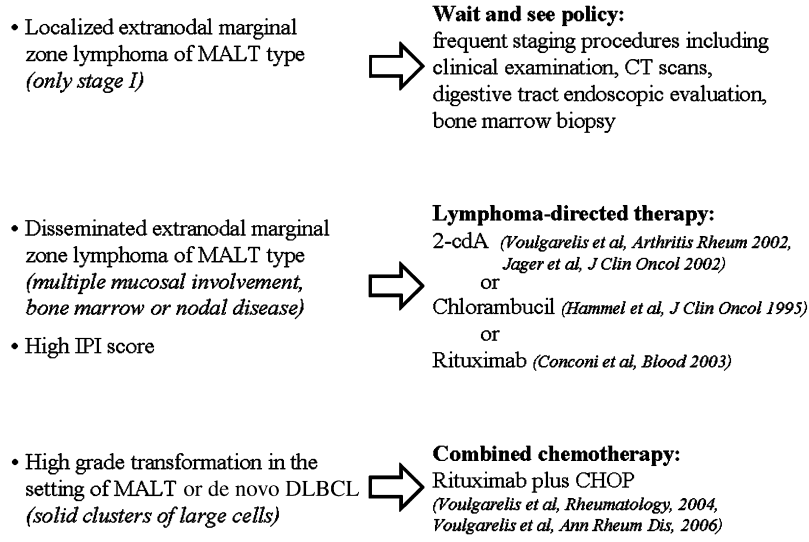

Fig. 3. Therapeutic guidelines for the management of SS-associated lymphomas. No established guidelines for the treatment of extranodal MALT lymphomas in SS have been published. This figure presents the authors' policy for the management of these indolent lymphomas. In localized disease, a policy of watchful waiting is used with close follow-up. If lymphoma is disseminated with nodal and bone marrow involvement, or if the patient has several risk factors according to the IPI, the authors administer single-agent chemotherapy such as chlorambucil, 2-CdA, or rituximab. Combination treatment with R-CHOP is the treatment of choice for patients who have SS with aggressive DLBCL.

a decrease of the circulating MMCs as well as an increase in C4 levels. Thus, R-CHOP seems to be effective in controlling both the autoimmune and neoplastic process in patients who have SS and DLBCL (see **Fig. 3**).

PROGNOSTIC FACTORS

The overall survival of patients who have MALT lymphoma is 85% to 95% at 5 years, with little difference between sites.[28,38,51] Regardless of site, approximately 25% to 35% of patients relapse after a CR, often late and to further extranodal or nodal sites, although significantly more relapses occur in nongastric cases than in gastric cases.[37,52] In MALT lymphomas in general, however, the 10-year expected survival rate is greater than 75%.[28] Several investigations have attempted to establish prognostic factors for poorer outcomes. Prognosis in MALT lymphoma has been reported to be influenced by prognostic factors for lymphoma in general, including poor performance status, bulky tumor, high levels of LDH, β2-microglobulin, and low serum albumin level.[48,53] The presence of a large-cell component at diagnosis also is associated with a poorer outcome.[48,53] The influence of systemic dissemination on survival is controversial, being significantly associated with poorer prognosis in some studies.[28,54] In one study, a high International Prognostic Index (IPI) score and lymph node involvement predicted poorer outcomes.[48] Interestingly the t(11;18) (q21;q21), a translocation specific to MALT-type lymphoma and detected in 18% to 24% of patients who have gastric MALT lymphoma, has been correlated with a resistance to *H. pylori* eradication therapy and to alkylating agents and but not to rituximab.[55–57] Recently, it has been reported that the frequency of translocations involving *MALT1* seems to be low in patients who have SS and extragastric MALT lymphomas.[58] In contrast, *MALT1* rearrangement frequently is present in patients who have gastric MALT lymphoma and SS, which may explain in part why gastric MALT lymphomas in patients who have SS are largely resistant to *H. pylori* eradication therapy.[58]

Although few studies investigating the mortality rate in primary SS have been reported, the development of lymphoma seems to be a major complication of this disease and is associated consistently with the presence of hypocomplementenia and MMC.[32–34] Skopouli and colleagues[32] studied the evolution of the clinical picture and laboratory profile, the incidence and predictors for systemic sequelae, and the impact of the disease on overall survival in a prospective cohort study that followed 261 Greek patients who had primary SS for a 10-year period. The results were compared with the general Greek population, adjusted for age and sex. According to this study the glandular manifestations of the syndrome typically were present at the time of diagnosis, whereas the serologic profile of the patients did not change substantially during the follow-up. The extraglandular manifestations could be divided into two different groups pertaining to disease outcome. The appearance of arthritis, Raynaud's phenomenon, interstitial nephritis, and lung and liver involvement early in the disease process usually had a favorable outcome. On the other hand, purpura, glomerulonephritis, decreased C4 complement levels, and MMC were identified as adverse prognostic factors. The overall mortality of patients who had primary SS compared with that of the general population was increased only in patients who had adverse predictors. This observation prompted the development of a predictive model that was used in a cohort of 723 consecutive patients who had primary SS.[33] During 4384 person-years of follow-up, 39 deaths (7 caused by lymphoma) and 38 diagnoses of lymphoproliferative disease were recorded. The standardized mortality ratio (SMR) was 1.15 (95% CI, 0.86–1.73) compared with the general population. Mortality rates were significantly higher in patients who presented with low C4 levels at the first study

visit (hazard ratio, 4.39). Based on these data, the authors' department suggested a predictive classification model that categorizes patients who have SS into two distinct groups, each carrying a different risk of developing lymphoma. Patients who have low C4 levels and/or palpable purpura are classified as high risk (type I SS); patients who do not have these predictive factors are classified as low risk (type II SS). The latter group constitutes 80% of all primary SS diagnoses.

Another study of 484 patients who had SS with a median 7-year follow-up reported 34 deaths, 6 of which were caused by lymphoproliferative disease.[59] Mortality predictor markers in this study were defined by low C3 and C4 levels. The SMR was 1.17 (95% CI, 0.81–1.63) compared with a lymphoproliferative disease cause-specific SMR of 7.89 (95% CI, 2.89–17.18), a result very similar to findings in the previous study. Yet another study of 218 patients who had SS demonstrated the association of low C4 levels with a low survival rate because of lymphoproliferative disease.[34] All these studies suggest that systemic manifestations as well as the serologic profile of SS presented at diagnosis determine the outcome of patients who have SS, with low levels of C4, C3, CH50, and cryoglobulinemia being the strongest predictors of lymphoproliferative disorders and mortality in SS.

SUMMARY

Patients who have SS and who have high risk factors such as palpable purpura, low C4 levels, and MMC constitute a separate subgroup that should be monitored more closely than other patients who have SS. These patients seem to have a strong predisposition for the development of lymphoproliferation, especially low-grade extranodal MALT lymphomas. Therefore, the clinical follow-up of patients who have SS should include routine complement determination and serum immunoelectrophoresis to detect the possible emergence of a monoclonal B-cell population susceptible to lymphoma development. Salivary MALT lymphomas in SS demonstrate a very indolent course with a long time to progression, even in the absence of treatment. Some patients develop disseminated disease, usually to other MALT sites or to lymph nodes. Histologically, low-grade MALT lymphomas are characterized by centrocyte-like B cells that surround reactive follicles and form characteristic lymphoepithelial lesions with adjacent epithelium. MALT lymphomas, despite presenting with stage IV disease in approximately one quarter of cases, usually have indolent course. Patients at high risk according to the IPI and those who have lymph node involvement at presentation, but not those with involvement of multiple MALT sites, have a worse prognosis. Localization can be an important factor because of organ-specific problems that require particular management strategies. Transformation of MALT lymphoma to DLBCL is characterized by a worse outcome. The optimal therapeutic strategy of MALT lymphomas is not yet defined.

REFERENCES

1. Leandro MJ, Isenberg DA. Rheumatic diseases and malignancy—is there an association? Scand J Rheumatol 2001;30:185–8.
2. Bunim JJ, Talal N. Development of malignant lymphoma in the course of Sjogren's syndrome. Trans Assoc Am Physicians 1963;76:45–56.
3. Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. Ann Intern Med 1978;89:888–92.
4. Moutsopoulos HM, Steinberg AD, Fauci AS, et al. High incidence of free monoclonal lambda light chains in the sera of patients with Sjogren's syndrome. J Immunol 1983;130:2663–5.

5. Tzioufas AG, Manoussakis MN, Costello R, et al. Cryoglobulinemia in autoimmune rheumatic diseases. Evidence of circulating monoclonal cryoglobulins in patients with primary Sjogren's syndrome. Arthritis Rheum 1986;29:1098–104.
6. Valesini G, Priori R, Bavoillot D, et al. Differential risk of non-Hodgkin's lymphoma in Italian patients with primary Sjogren's syndrome. J Rheumatol 1997;24: 2376–80.
7. Zulman J, Jaffe R, Talal N. Evidence that the malignant lymphoma of Sjogren's syndrome is a monoclonal B-cell neoplasm. N Engl J Med 1978;299:1215–20.
8. Schmid U, Helbron D, Lennert K. Development of malignant lymphoma in myoepithelial sialadenitis (Sjogren's syndrome). Virchows Arch A Pathol Anat Histol 1982;395:11–43.
9. Pisa EK, Pisa P, Kang HI, et al. High frequency of t(14;18) translocation in salivary gland lymphomas from Sjogren's syndrome patients. J Exp Med 1991;174:1245–50.
10. Sutcliffe N, Inanc M, Speight P, et al. Predictors of lymphoma development of primary Sjogren's syndrome. Semin Arthritis Rheum 1998;28:80–7.
11. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med 2005;165:2337–44.
12. Voulgarelis M, Dafni UG, Isenberg DA, et al. Malignant lymphoma in primary Sjogren's syndrome: a multicenter, retrospective, clinical study by the European concerted action on Sjogren's syndrome. Arthritis Rheum 1999;42:1765–72.
13. Royer B, Cazals-Hatem D, Sibilia J, et al. Lymphomas in patients with Sjogren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites and are not associated with viruses. Blood 1997;90:766–75.
14. Mariette X. Lymphomas in patients with Sjogren's syndrome: review of the literature and physiopathologic hypothesis. Leuk Lymphoma 1999;33(1–2):93–9.
15. Ambrosetti A, Zanotti R, Pattaro C, et al. Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with Sjoegren syndrome or hepatitis C virus infection. Br J Haematol 2004;126:43–9.
16. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst 2006;98:51–60.
17. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997;89:3909–18.
18. Müller AM, Ihorst G, Mertelsmann R, et al. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. Ann Hematol 2005;84:1–12.
19. Pelstring RJ, Essell JH, Kurtin PJ, et al. Diversity of organ site involvement among malignant lymphomas of mucosa-associated tissues. Am J Clin Pathol 1991;96:738–45.
20. Dogan A, Du M, Koulis A, et al. Expression of lymphocyte homing receptors and vascular addressins in low-grade gastric B-cell lymphomas of mucosa-associated lymphoid tissue. Am J Pathol 1997;151:1361–9.
21. Isaacson PG, Spencer J. Malignant lymphoma of mucosa-associated lymphoid tissue. Histopathology 1987;11:445–62.
22. Harris NL, Isaacson PG. What are the criteria for distinguishing MALT from non-MALT lymphoma at extranodal sites? Am J Clin Pathol 1999;111(1 Suppl 1):S126–32.
23. Hyjek E, Smith WJ, Isaacson PG. Primary B-cell lymphoma of salivary glands and its relationship to myoepithelial sialadenitis. Hum Pathol 1988;19:766–76.
24. Diss TC, Wotherspoon AC, Speight P, et al. B-cell monoclonality, Epstein Barr virus, and t(14;18) in myoepithelial sialadenitis and low-grade B-cell MALT lymphoma of the parotid gland. Am J Surg Pathol 1995;19:531–6.

25. Rossi D, Gaidano G. Molecular heterogeneity of diffuse large B-cell lymphoma: implications for disease management and prognosis. Hematology 2002;7:239–52.
26. Du MQ, Xu CF, Diss TC, et al. Intestinal dissemination of gastric mucosa-associated lymphoid tissue lymphoma. Blood 1996;88:4445–51.
27. Neumeister P, Hoefler G, Beham-Schmid C, et al. Deletion analysis of the p16 tumor suppressor gene in gastrointestinal mucosa-associated lymphoid tissue lymphomas. Gastroenterology 1997;112:1871–5.
28. Thieblemont C, Berger F, Dumontet C, et al. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood 2000;95:802–6.
29. Anderson LG, Talal N. The spectrum of benign to malignant lymphoproliferation in Sjogren's syndrome. Clin Exp Immunol 1972;10:199–221.
30. Tzioufas AG, Boumba DS, Skopouli FN, et al. Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjogren's syndrome. Arthritis Rheum 1996;39:767–72.
31. Walters MT, Stevenson FK, Herbert A, et al. Urinary monoclonal free light chains in the primary Sjogren's syndrome: an aid to the diagnosis of malignant lymphoma. Ann Rheum Dis 1986;45:210–9.
32. Skopouli FN, Dafni U, Ioannidis JP, et al. Clinical evolution, and morbidity and mortality of primary Sjogren's syndrome. Semin Arthritis Rheum 2000;29:296–304.
33. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjogren's syndrome. Arthritis Rheum 2002;46:741–7.
34. Ramos-Casals M, Brito-Zeron P, Yague J, et al. Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjogren's syndrome. Rheumatology (Oxford) 2005;44:89–94.
35. Theander E, Henriksson G, Ljungberg O, et al. Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 2006;65:796–803.
36. Anaya JM, McGuff HS, Banks PM, et al. Clinicopathological factors relating malignant lymphoma with Sjogren's syndrome. Semin Arthritis Rheum 1996;25: 337–46.
37. Zinzani PL, Magagnoli M, Galieni P, et al. Nongastrointestinal low-grade mucosa-associated lymphoid tissue lymphoma: analysis of 75 patients. J Clin Oncol 1999; 17:1254–8.
38. Zucca E, Conconi A, Pedrinis E, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Blood 2003;101:2489–95.
39. Voulgarelis M, Moutsopoulos HM. Malignant lymphoma in primary Sjogren's syndrome. Isr Med Assoc J 2001;3:761–6.
40. Hammel P, Haioun C, Chaumette MT, et al. Efficacy of single-agent chemotherapy in low-grade B-cell mucosa-associated lymphoid tissue lymphoma with prominent gastric expression. J Clin Oncol 1995;13:2524–9.
41. Conconi A, Martinelli G, Thiéblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood 2003;102:2741–5.
42. Jäger G, Neumeister P, Brezinschek R, et al. Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type with cladribine: a phase II study. J Clin Oncol 2002;20:3872–7.
43. Zinzani PL, Stefoni V, Musuraca G, et al. Fludarabine-containing chemotherapy as frontline treatment of nongastrointestinal mucosa-associated lymphoid tissue lymphoma. Cancer 2004;100:2190–4.

44. Voulgarelis M, Petroutsos G, Moutsopoulos HM, et al. 2-chloro-2-deoxyadenosine in the treatment of Sjogren's syndrome-associated B cell lymphoproliferation. Arthritis Rheum 2002;46:2248–9.
45. Hussell T, Isaacson PG, Crabtree JE, et al. Helicobacter pylori-specific tumour-infiltrating T cells provide contact dependent help for the growth of malignant B cells in low-grade gastric lymphoma of mucosa-associated lymphoid tissue. J Pathol 1996;178:122–7.
46. Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum 2005; 52:2740–50.
47. Pijpe J, van Imhoff GW, Vissink A, et al. Changes in salivary gland immunohistology and function after rituximab monotherapy in a patient with Sjogren's syndrome and associated MALT lymphoma. Ann Rheum Dis 2005;64:958–60.
48. Thieblemont C, Bastion Y, Berger F, et al. Mucosa-associated lymphoid tissue gastrointestinal and nongastrointestinal lymphoma behavior: analysis of 108 patients. J Clin Oncol 1997;15:1624–30.
49. Voulgarelis M, Giannouli S, Anagnostou D, et al. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. Rheumatology (Oxford) 2004;43:1050–3.
50. Voulgarelis M, Giannouli S, Tzioufas AG, et al. Long-term remission of Sjogren's syndrome-associated aggressive B-cell non-Hodgkin's lymphomas following administration of combined B-cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Ann Rheum Dis 2006;65:1033–7.
51. Zucca E, Bertoni F, Roggero E, et al. The gastric marginal zone B-cell lymphoma of MALT type. Blood 2000;96:410–9.
52. Raderer M, Streubel B, Woehrer S, et al. High relapse rate in patients with MALT lymphoma warrants lifelong follow-up. Clin Cancer Res 2005;11:3349–52.
53. Radaszkiewicz T, Dragosics B, Bauer P. Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: factors relevant to prognosis. Gastroenterology 1992;102:1628–38.
54. Montalbán C, Castrillo JM, Abraira V, et al. Gastric B-cell mucosa-associated lymphoid tissue (MALT) lymphoma. Clinicopathological study and evaluation of the prognostic factors in 143 patients. Ann Oncol 1995;6:355–62.
55. Lévy M, Copie-Bergman C, Gameiro C, et al. Prognostic value of translocation t(11;18) in tumoral response of low-grade gastric lymphoma of mucosa-associated lymphoid tissue type to oral chemotherapy. J Clin Oncol 2005;23:5061–6.
56. Liu H, Ruskon-Fourmestraux A, Lavergne-Slove A, et al. Resistance of t(11;18) positive gastric mucosa-associated lymphoid tissue lymphoma to Helicobacter pylori eradication therapy. Lancet 2001;357(9249):39–40.
57. Martinelli G, Laszlo D, Ferreri AJ, et al. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy. J Clin Oncol 2005;23:1979–83.
58. Streubel B, Huber D, Wohrer S, et al. Frequency of chromosomal aberrations involving MALT1 in mucosa-associated lymphoid tissue lymphoma in patients with Sjogren's syndrome. Clin Cancer Res 2004;10:476–80.
59. Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjogren's syndrome: a prospective cohort study. Arthritis Rheum 2004;50:1262–9.

Relationship of Sjögren's Syndrome to Other Connective Tissue and Autoimmune Disorders

Elke Theander, MD, PhD*, Lennart T.H. Jacobsson, MD, PhD

KEYWORDS

- Secondary Sjögren's syndrome
- Systemic autoimmune diseases
- Systemic lupus erythematosus
- Rheumatoid arthritis • Overlap • Associated diseases

Sjögren's syndrome, which may be the most common connective tissue disease that appears in association with other autoimmune disorders, has received the attributes *primary*, when it appears alone, or *secondary*, when it appears in association with another well-defined disease.[1] The terms *primary* and *secondary* have been used since 1965[1] and have been supported by studies demonstrating distinct immunologic differences between Sjögren's syndrome patients with rheumatoid arthritis and those without rheumatoid arthritis.[2–4] Such clear distinctions have, however, not been documented for associations with other autoimmune diseases. Thirty percent of primary Sjögren's syndrome patients have been shown to suffer from other autoimmune conditions, which in about equal numbers develop either before or after the Sjögren's syndrome diagnosis, according to a recent cohort study from Britain.[5] Likewise, 30% of the primary systemic lupus erythematosus patients from the same center developed secondary autoimmune diseases.[6,7] Clustering of autoimmune diseases, including Sjögren's syndrome, in the same patients seems independent of ethnicity.[7,8] The most recent classification criteria that define primary and secondary Sjögren's syndrome are presented in **Box 1**.[9]

According to the most common interpretation of the present classification criteria for Sjögren's syndrome, the term *secondary* is used for all cases concomitantly present with another connective tissue disease, even in cases in which Sjögren's

Department of Rheumatology, Malmö University Hospital, Lund University, 20502 Malmö, Sweden
* Corresponding author.
E-mail address: elke.theander@med.lu.se (E. Theander).

Rheum Dis Clin N Am 34 (2008) 935–947
doi:10.1016/j.rdc.2008.08.009 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

Box 1
Revised international classification criteria for Sjögren's syndrome

Revised criteria

1. Ocular symptoms: a positive response to at least one of the following questions:

   Have you had daily, persistent, troublesome dry eyes for more than 3 months?

   Do you have a recurrent sensation of sand or gravel in the eyes?

   Do you use tear substitutes more than three times a day?

2. Oral symptoms: a positive response to at least one of the following questions:

   Have you had a daily feeling of dry mouth for more than 3 months?

   Have you had recurrently or persistently swollen salivary glands as an adult?

   Do you frequently drink liquids to aid in swallowing dry food?

3. Ocular signs: objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

   Schirmer's I test, performed without anesthesia (5 mm in 5 minutes)

   Rose bengal score or other ocular dye score (4 or more according to van Bijsterveld's scoring system)

4. Histopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score of 1 or more, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue

5. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

   Unstimulated whole salivary flow ($\geq$1.5 mL in 15 minutes)

   Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts

   Salivary scintigraphy showing delayed uptake, reduced concentration, or delayed excretion of tracer

6. Autoantibodies: presence in the serum of one or both of the following autoantibodies:

   Antibodies to Ro(Sjögren's syndrome A) antigens

   Antibodies to La(Sjögren's syndrome B) antigens

Revised rules for classification

For primary Sjögren's syndrome
In patients without any potentially associated disease, primary Sjögren's syndrome may be defined as follows:

The presence of any four of the six items is indicative of primary Sjögren's syndrome, as long as either histopathology or serology is positive

The presence of any three of the four objective criteria items (ie, items 3, 4, 5, and 6)

The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiologic survey

For secondary Sjögren's syndrome
In patients with a potentially associated disease (eg, another well-defined connective tissue disease), the presence of item 1 or item 2 plus any two from among items 3, 4, and 5 may be considered as indicative of secondary Sjögren's syndrome

Exclusion criteria:

- Past head and neck radiation treatment
- Hepatitis C infection
- AIDS
- Pre-existing lymphoma
- Sarcoidosis
- Graft versus host disease
- Use of anticholinergic drugs (since a time shorter than fourfold the half-life of the drug)

From Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61(6):557; with permission.

syndrome was present years before the other ''primary'' disorder. The possibility of association or overlap of two autoimmune conditions is not taken into account. However, some investigators would use the term *primary Sjögren's syndrome* for patients who fulfill the criteria for primary Sjögren's syndrome despite the presence of other autoimmune disease. These investigators would thus introduce the concept of overlap or associated diseases.[10–12] Differentiation of isolated or associated primary Sjögren's syndrome and secondary Sjögren's syndrome may be meaningful. The ''secondary'' classification would imply that the impact of the Sjögren's component would be of minor importance with regard to the patient's outcome, as most often seen in rheumatoid arthritis. These patients usually do not express the full-blown disease but rather a restricted sicca syndrome. Lumping together all forms of secondary, associated, or overlapping Sjögren's syndrome into secondary Sjögren's syndrome may prevent progress in research that targets pathomechanisms in these overlap syndromes.

Some investigators have tried to use histopathology and genetic markers to differentiate Sjögren's syndrome associated with systemic lupus erythematosus from Sjögren's syndrome secondary to systemic lupus erythematosus.[13] Meanwhile, increasing evidence shows the similarity of genetic signatures, especially within the interferon system, between Sjögren's syndrome and systemic lupus erythematosus.[14–16] There is clearly a lack of understanding of the mechanisms that drive the immune system towards the expression of subclinical forms, single, or multiple autoimmune diseases in the same host.

Sjögren's syndrome has been described in association with the majority of the major connective tissue diseases and it has been proposed to be present in 20% of persons with other systemic autoimmune diseases.[17] Lazarus and Isenberg[5] found that 13 other autoimmune diseases developed either before or after the Sjögren's syndrome diagnosis in 114 primary Sjögren's syndrome patients followed over a mean of 10.5 years. These disorders included renal tubular acidosis, glomerulonephritis, pulmonary fibrosis, and idiopathic thrombocytopenia. Others have interpreted these disorders as part of Sjögren's syndrome itself. Additional autoimmune disorders identified in the report by Lazarus and Isenberg[5] were autoimmune thyroid and liver diseases, celiac disease, myositis, scleroderma, pernicious anemia and discoid lupus. Six percent had 2 and 2% had 3 additional autoimmune conditions among those mentioned above. Case reports have been published describing Sjögren's syndrome in patients with multiple autoimmune diseases, such as a recent report on the concomitant presence of 5 autoimmune diseases.[18] Cases like this are clearly an expression of a more widespread disturbance in the affected individual's immune system. Generally,

organ-specific and non–organ-specific autoimmune diseases seem to be associated in high frequency with Sjögren's syndrome. Sjögren's syndrome itself is sometimes portrayed as a syndrome that presents as an organ-specific (glandular) autoimmune inflammation subsequently expanding into a systemic disease. Thus the disease not only links autoimmunity with infection, and autoimmunity with malignancy, but it also links organ-specific autoimmunity with systemic autoimmunity. The concomitant presence of this spectrum of autoimmune manifestations in one individual implies a common genetic, hormonal, infectious, or other environmental etiology, or a combination of these. The presence of multiple autoantibodies, which is considered typical of other systemic autoimmune disease, does not in most cases of primary Sjögren's syndrome result in development of clinical significant disease but may influence the pattern of disease expression in primary Sjögren's syndrome itself.[19]

In describing the present knowledge related to Sjögren's syndrome in association with other autoimmune diseases, we refer mainly to publications using the most recent approach of classifying Sjögren's syndrome,[9] namely requiring a detectable objective manifestation of autoimmunity in addition to sicca syndrome. Thus, sicca syndromes associated with such diseases as fibromyalgia, chronic fatigue syndrome, pain disorders, and psychologic distress of other causes are excluded. Accordingly, all sicca syndromes caused by medication, malignancies, sarcoidosis, and infections are excluded from the present overview.

SYSTEMIC LUPUS ERYTHEMATOSUS

Of all the associations between Sjögren's syndrome and other connective tissue diseases the one with systemic lupus erythematosus has probably received most attention in scientific publications. The first such description dates back to 1959.[20] Sjögren's syndrome presenting in association with systemic lupus erythematosus is usually described as quite similar to the primary form, with the same frequency of autoantibodies, nonexocrine manifestations, and severity of signs and symptoms.

Two recent and more in-depth studies of clinical, serologic, pathologic, and immunogenetic features of these patients have been performed. Szanto[12] described 56 patients from Hungary with associated Sjögren's syndrome and systemic lupus erythematosus (SS-SLE), compared with 50 patients with systemic lupus erythematosus only and 50 patients with Sjögren's syndrome only. Despite an exhausting description of all possible clinical, immunologic, and genetic parameters, the paper did not reveal many unexpected differences among the three groups. Along with central nervous system involvement and anti-DNA antibodies, antiphospholipid antibodies were found more frequently in SS-SLE than in isolated Sjögren's syndrome. In terms of hematological disturbances, SS-SLE seemed more similar to systemic lupus erythematosus than to primary Sjögren's syndrome. Surprisingly, associated thyroiditis was more common in patients with SS-SLE than in either patients with Sjögren's syndrome alone or in patients with systemic lupus erythematosus alone, signaling the propensity to widespread autoimmune dysregulation in these overlap cases. SS-SLE patients also had the highest expression of autoantibodies to various antigens. Convincing differences in major histocompatibility complex alleles or salivary gland histology could not be detected among the groups. In a report from Athens, 26 out of 283 systemic lupus erythematosus patients (9.2%) fulfilled the criteria for secondary Sjögren's syndrome.[13] Most of these patients had been followed for sicca complaints years before the systemic lupus erythematosus diagnosis was established. Only 4 patients developed Sjögren's syndrome after the diagnosis of systemic lupus erythematosus. The Hungarian study classified the patients as having

associated and not secondary Sjögren's syndrome, while the Greek study labeled the patients as having secondary Sjögren's syndrome. Still, the results were similar. A recent paper from China identified 35 (6.5%) of 542 consecutive systemic lupus erythematosus patients having Sjögren's syndrome.[21] These were compared with 507 patients without Sjögren's syndrome. With the exception of a lower frequency of renal involvement, older age in SS-SLE, and a different autoantibody profile, no relevant differences were detected between groups. The similarity of Sjögren's syndrome with late-onset systemic lupus erythematosus has also been documented by others[22] and Ramos-Casals and colleagues[23] proposed to label these patients as having primary Sjögren's syndrome in the absence of features highly suggestive of systemic lupus erythematosus (discoid lupus, anti-Sm antibodies, high titers of anti-DNA, central nervous system involvement, hemolytic anemia, or proliferative glomerulonephritis). Lazarus and Isenberg[5] could not detect any patients within their Sjögren's syndrome cohort who later on developed systemic lupus erythematosus. In the investigators' systemic lupus erythematosus cohort, around 12% of patients also had Sjögren's syndrome.[6,7] Scofield and colleagues[24] identified 169 cases of Sjögren's syndrome among 1138 patients with systemic lupus erythematosus (prevalence 14.9%). In our own cohort of patients with a diagnosis of primary Sjögren's syndrome, according to the American European Consensus Criteria (AECC), we found that after 10 years of follow-up, 15% of the patients fulfilled at least four items out of the systemic lupus erythematosus criteria and thus would formally qualify to be classified as systemic lupus erythematosus. Predictors of this development were lower age, lower C3 concentration, higher level of IgG, and, surprisingly, the presence of anti–Sjögren's syndrome B at the time of diagnosis of primary Sjögren's syndrome (**Table 1**).[25]

SLE-SS patients seem to be very similar to primary Sjögren's syndrome patients. The systemic lupus erythematosus in these cases, when associated with Sjögren's syndrome, frequently is characterized by milder disease compared with systemic lupus erythematosus without Sjögren's syndrome, illustrated by a lower risk of severe renal disease and thrombocytopenia.[13] However, they are more likely to have Raynaud phenomenon and arthritis,[13] implying a possible protective effect of the Sjögren's syndrome phenotype with regard to the development of a full-blown lupus syndrome. One study, however, discovered an increased morbidity and mortality in systemic lupus erythematosus associated with other autoimmune diseases because of such events as thrombosis and lymphoma.[7] Fatigue may be more prominent in systemic lupus erythematosus patients who develop features of Sjögren's syndrome.[26] Again these findings underscore the similarity between SLE-SS patients and patients with primary Sjögren's syndrome, a disease with relatively mild symptoms in most cases, provided the patient does not develop lymphoma. The occurrence of an overlap between SS and SLE affects the age of both diseases earlier than would be expected for SS and later for SLE. Sjögren's syndrome may delay the development of systemic lupus erythematosus, as in SS-SLE overlap where the systemic lupus erythematosus usually displays a later onset than in systemic lupus erythematosus without Sjögren's syndrome.[12,13,21,25] Sjögren's syndrome in association with systemic lupus erythematosus appears earlier than isolated Sjögren's syndrome in these studies. With the currently available knowledge, it seems impossible to meaningfully differentiate between associated and secondary Sjögren's syndrome in systemic lupus erythematosus. Likewise, no one tell at the present time whether Sjögren's syndrome and systemic lupus erythematosus are separate disorders or variants of the same disease. In 1959, Heaton[20] proposed that Sjögren's syndrome may be a chronic and relatively benign form of systemic lupus erythematosus. In practical terms, this academic problem does not influence management of the affected patient. Such

Table 1
Predictors for subsequent systemic lupus erythematosus association in primary Sjögren's syndrome

	Sjögren's Syndrome and <4 Systemic Lupus Erythematosus Criteria[a]	Sjögren's Syndrome and ≥4 Systemic Lupus Erythematosus Criteria[a]	*P* Value
Age at Sjögren's syndrome diagnosis (y)	54.7 (14.5)	45.0 (11.6)	.006
Female (%)	95	94	.59
Schirmer-1 test (mm/5 min)	5.6 (6.1)	6.1 (6.2)	.79
Van Bijsterveld score	9.1 (5.4)	9.7 (5.6)	.70
Unstimulated whole salivary flow (mL/15 min)	0.44 (0.60)	0.57 (1.14)	.65
Salivary gland biopsy with focus score >1 (%)	91	86	.63
Anti-Ro/Sjögren's syndrome A (%)[b]	62	82	.16
Anti-La/Sjögren's syndrome B (%)[b]	43	77	.02
Rheumatoid factor (%)	65	77	.41
Antinuclear antibody test (%)	85	100	.21
C3 (g/L)[b]	1.00 (0.31)	0.76 (0.25)	.002
C4 (g/L)[b]	0.26 (0.15)	0.20 (0.10)	.06
IgG (g/L)[b]	17.6 (7.95)	25.68 (11.23)	.01

[a] Values are mean (SD).
[b] At Sjögren's syndrome diagnosis.
From Theander E, Jacobsson LTH. Features of systemic lupus erythematosus in patients with primary Sjögren's syndrome. A cross-sectional analysis of the 11 items of the SLE criteria set and the levels of complement factors C3 and C4 in 100 primary Sjögren's syndrome patients. Lupus. 2005;14(3):S231; with permission.

management will be guided by disease activity and type and severity of organ manifestations.

SYSTEMIC SCLEROSIS

Complaints of sicca symptoms are common among patients with systemic sclerosis. Fibrotic changes of the salivary glands are frequently found and result in oral dryness. Older publications describe a prevalence of ''secondary'' Sjögren's syndrome in 17% to 29% of systemic sclerosis patients; extremes of 1% and 90% have been reported.[27,28] Only a few papers are available analyzing the frequency and characteristics of Sjögren's syndrome in systemic sclerosis, according to the AECC.[11,29] Sicca syndrome with subjective dryness has been found in 68% and, of these, 55% had fibrosis in salivary gland biopsies.[29] Fourteen percent of the patients (19 of 133 patients) in the same survey fulfilled the AECC criteria for secondary Sjögren's syndrome.[29] Sjögren's syndrome associated with systemic sclerosis seems to express much the same features as primary Sjögren's syndrome according to a study of 27 patients with both Sjögren's syndrome and systemic sclerosis compared with 202 patients

with Sjögren's syndrome only. While 84% had classical focal sialadenitis with focus score of 1 or more, only 18% had concomitant fibrosis. In terms of complications, primary Sjögren's syndrome showed a somewhat increased prevalence of cryoglobulinemia, while Sjögren's syndrome associated with systemic sclerosis more often was complicated by peripheral neuropathy and additional autoimmune disease or autoantibodies, not typical for either primary Sjögren's syndrome or systemic sclerosis. On the other hand, Sjögren's syndrome may be protective against systemic sclerosis–associated pulmonary fibrosis, a finding in two recent French studies.[11,29] Limited systemic sclerosis was predominantly associated with Sjögren's syndrome in these studies (81% and 95% respectively).[11,29] In summary, the restricted data on Sjögren's syndrome in systemic sclerosis indicate that symptoms of dryness are due mainly to fibrosis of the glands and thus due to scleroderma itself, while a limited number of patients reveal associated Sjögren's syndrome manifesting features of primary Sjögren's syndrome. There also appears to be a protective influence regarding the risk of developing pulmonary fibrosis. Sjögren's syndrome patients who present with anticentromere antibodies and who do not fulfill criteria for systemic sclerosis (4.7% in a recent French survey,[30] 7.8% in our own cohort [unpublished data]) represent a subgroup of primary Sjögren's syndrome with overrepresentation of features frequently associated with systemic sclerosis, such as Raynaud phenomenon. These patients also display a higher prevalence of peripheral neuropathy and frequent association with other autoantibodies or autoimmune diseases, especially primary biliary cirrhosis (PBC).[30] Anticentromere antibodies may predict development of systemic sclerosis later on,[19] though this could not be confirmed by all investigators.[30]

MIXED CONNECTIVE TISSUE DISEASE

There are no studies of patients with mixed connective tissue disease (MCTD) that analyze the prevalence of Sjögren's syndrome. Lazarus and Isenberg[5] did not note the development of MCTD in primary Sjögren's syndrome. Case reports of overlap between the two disorders exist.[18] The prevalence of antiribonucleoprotein autoantibodies in the absence of coexisting MCTD has been reported to be 4%[19] in primary Sjögren's syndrome.

INFLAMMATORY MUSCLE DISEASE

The presence of myositis in primary Sjögren's syndrome was studied by two groups in recent years: While Lazarus and Isenberg[5] detected only 1.8% of myositis overlap in their British cohort of Sjögren's syndrome patients, Lindvall and colleagues[31] found that 14% of their Sjögren's syndrome patients suffer from myositis, when muscle involvement was studied both clinically and histologically. There are no reports from larger myositis cohorts that define the prevalence of Sjögren's syndrome in primary myositis. Some case reports exist on the coexistence of inclusion body myositis and Sjögren's syndrome.[32,33] These Sjögren's syndrome–associated inclusion body myositis cases seem to differ from primary inclusion body myositis in demonstrating a better response to immunosuppressive therapy. We have recently observed an association of classical dermatomyositis, systemic lupus erythematosus, and Sjögren's syndrome (unpublished data). Generally, myositis is accepted as a relatively rare complication of primary Sjögren's syndrome as opposed to the existence of two associated diseases.

AUTOIMMUNE LIVER DISEASES

Autoimmune chronic active hepatitis (CAH) and PBC are autoimmune liver diseases frequently thought to be associated with Sjögren's syndrome. Again, older publications on this association are difficult to interpret because of the inconsistent definition of Sjögren's syndrome. In 1994, we found PBC in 9% and CAH in 4% of our primary Sjögren's syndrome patients.[34] However, the definition of Sjögren's syndrome according to the Copenhagen criteria[35] does not allow differentiation between sicca syndrome due to PBC or CAH and primary Sjögren's syndrome associated with these disorders. A new survey in 2008 revealed only 2 cases of PBC and 1 case of CAH among 109 consecutive primary Sjögren's syndrome patients, while another 2 patients with PBC had severe sicca syndrome without fulfilling the AECC criteria for primary Sjögren's syndrome (unpublished observation). These data are in concordance with Lazarus and Isenberg's publication of additional autoimmune diseases in primary Sjögren's syndrome, where 2 out of 114 primary Sjögren's syndrome patients developed PBC and 1 CAH, while another 2 patients already had a diagnosis of CAH before their Sjögren's syndrome diagnosis.[5] Unfortunately, this paper from 2005 uses the 1993 European criteria for Sjögren's syndrome,[36] making it difficult to evaluate the exact significance of these findings, even though 84% of patients had autoimmune sialadenitis in the salivary gland biopsy. In 1993, a Japanese nationwide survey of autoimmune hepatitis found that 9% (80 of 817) of the patients had associated Sjögren's syndrome.[37] A more recent Japanese paper demonstrated that, of those Sjögren's syndrome patients with clinical liver disease who underwent liver biopsy, 47% had CAH and 35% had PBC, while another 18% had other nonspecific liver inflammation.[38] A recent paper from Mexico detected PBC in 6% and CAH in 2% of 82 patients with primary Sjögren's syndrome not suffering from virus hepatitis.[39] The extent of association between autoimmune liver disease and Sjögren's syndrome shows great variability, which may reflect different environmental and genetic backgrounds in different continents.

AUTOIMMUNE THYROID DISEASE

The overlap between systemic autoimmune diseases and autoimmune thyroid disease is well known. Most studies, however, are from a time before the publication of the AECC criteria for primary Sjögren's syndrome and thus difficult to compare. Among more recent publications, the prevalence of autoimmune thyroid disease was 10% among 400 patients with primary Sjögren's syndrome followed in Hungary. Seven percent had Hashimoto thyroiditis and 3% Graves disease, about twice as frequent as in the systemic lupus erythematosus cohort from the same center and more than 150 times higher than in the general nonautoimmune Hungarian population.[40] Patients with autoimmune thyroid diseases had other systemic autoimmune diseases in 30% of the cases. Sjögren's syndrome was the most common associated systemic autoimmune disease (9.4%) followed by mixed connective tissue disease. In contrast, a smaller study from Turkey could not confirm an increased prevalence of autoimmune thyroid diseases or even antithyroid autoantibodies in Sjögren's syndrome (n = 53).[41] On the other hand, Scofield and colleagues[24] reported that 30% of SLE-SS patients (n = 169) had autoimmune thyroid disease and, of 44 primary Sjögren's syndrome patients who were relatives of systemic lupus erythematosus patients, 36% had autoimmune thyroid disease. The investigators conclude that autoimmune thyroid disease is overrepresented in systemic lupus erythematosus patients with Sjögren's syndrome as compared with systemic lupus erythematosus patients without Sjögren's syndrome and relatives

of systemic lupus erythematosus patients who have Sjögren's syndrome but not systemic lupus erythematosus. This strong association of autoimmune thyroid disease coincidental with SLE-SS overlap had been described earlier from Southern Sweden.[42] In our own primary Sjögren's syndrome cohort, 23% of 108 patients studied in a recent cross-sectional survey had thyroid-related autoantibodies (unpublished observation). Proposed mechanisms for the coincidence of autoimmune thyroid disease and Sjögren's syndrome or systemic lupus erythematosus include genetic factors (HLA antigen class II allele similarity) and crossreactivity of antithyroid autoantibodies or autoreactive T cells with other tissues, such as common epithelial antigens.[40] In summary, the most recent research seems to support a strong association of Sjögren's syndrome with thyroid autoimmunity, frequently in combination with further autoimmune diseases, such as autoimmune liver disease or systemic lupus erythematosus.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is frequently associated with both sicca symptoms and true secondary Sjögren's syndrome.[9] The association between the two disorders has already been observed by Henrik Sjögren himself.[43] Symptoms of dryness and objective signs of gland dysfunction are only weakly correlated,[44,45] similar to the situation in normal populations.[46,47] Sjögren's syndrome is usually included among extra-articular manifestations of rheumatoid arthritis. The prevalence varies considerably, depending on the definition of secondary Sjögren's syndrome, disease duration, and geographic region.[48] In Spain, the cumulative prevalence of secondary Sjögren's syndrome in rheumatoid arthritis was 17% at 10 years' disease duration and as much as 25% after 30 years when actively looked for and diagnosed by presence of objective and subjective sicca manifestations in the eyes or mouth.[49] This relationship to disease duration was not confirmed in the Norwegian study by Uhlig and colleagues,[45] but was present in the Early Rheumatoid Arthritis Study from the United Kingdom.[48,50] An Austrian study reported a 22% prevalence of sicca syndrome among patients with rheumatoid arthritis.[51] While anti–cyclic citrullinated peptide-2 autoantibodies are associated with severe extra-articular manifestations of rheumatoid arthritis, such as pulmonary fibrosis and serositis, the occurrence of secondary Sjögren's syndrome was mainly predicted by the presence of high titers of rheumatoid factor.[52] The severity of associated dry eye disease seems independent of the rheumatoid arthritis disease activity in Japanese patients[53] and Norwegian patients.[45] The latter, however, showed a correlation between reduced saliva production and rheumatoid arthritis disease activity.[45] The impact of concomitant secondary Sjögren's syndrome on the course of rheumatoid arthritis has not been studied extensively. However, more intense lethargy, fatigue, and a twofold risk of non-Hodgkin's lymphoma has been described compared with rheumatoid arthritis patients without Sjögren's syndrome.[54] Lymphoma development and pulmonary disease may contribute to a trend toward increased premature mortality in rheumatoid arthritis patients with secondary Sjögren's syndrome.[55,56]

OTHER DISEASES

Infectious agents are known to be capable of inducing autoimmune phenomena, such as autoantibody production, arthritis, and vasculitis. In the genetically predisposed host, an additional exogenous stimulus may induce loss of immunologic tolerance. There is an ongoing discussion in the literature regarding the association of hepatitis C with Sjögren's syndrome (see separate chapter on this issue). Other potentially associated autoimmune disease states include celiac disease,[57–59] Felty syndrome,[60]

general immunodeficiency states,[61] C1q deficiency,[62] and antiphospholipid antibody syndrome.[63]

SUMMARY

Sjögren's syndrome is a systemic autoimmune disease frequently associated with other organ-specific or systemic autoimmune diseases. The association is well described for systemic lupus erythematosus and rheumatoid arthritis. For most other diseases, references in the literature are more sporadic or based on case reports or case series. Sjögren's syndrome may appear before or after the associated disease. A common genetic background and additional immunogenetic, environmental, or hormonal factors may be suspected to drive the clustering of autoimmune disorders. The mechanisms for these events are, however, incompletely understood. The current classification criteria designate these cases as secondary Sjögren's syndrome. A differentiation of Sjögren's syndrome into secondary, associated, or overlap cases does not appear at this time to be supported by sufficient data elucidating pathogenic features unique to autoimmune syndrome clusters. Nonetheless, Sjögren's syndrome when present in addition to another systemic autoimmune disease seems to influence the character and phenotype of the disease, by either aggravating (eg, fatigue or lymphoma in rheumatoid arthritis) or ameliorating (eg, less renal or central nervous system disease in lupus) the course, but the impact of Sjögren's syndrome on long-term outcome of other autoimmune diseases requires further investigation.

Thus, the key points of this article are:

- Sjögren's syndrome is frequently associated with other autoimmune diseases.
- Most data relates to rheumatoid arthritis and systemic lupus erythematosus in association with Sjögren's syndrome, but data are scarce on the impact of Sjögren's syndrome on long-term outcome in these diseases.
- The terminology of *secondary*, *associated*, and *overlap* Sjögren's syndrome needs further clarification.

REFERENCES

1. Bloch KJ, Buchanan WW, Wohl MJ, et al. Sjögren's syndrome, a clinical, pathological and serological study of sixty-two cases. Medicine 1965;44:187–231.
2. Moutsopoulos HM, Webber BL, Vlagopoulos TP, et al. Differences in the clinical manifestations of sicca syndrome in the presence and absence of rheumatoid arthritis. Am J Med 1979;66:733–6.
3. Manthorpe R, Morling N, Platz P, et al. HLA-D antigen frequencies in Sjögren's syndrome: differences between the primary and the secondary form. Scand J Rheumatol 1981;10:124–8.
4. Bodeutsch C, de Wilde PC, Kater L, et al. Quantitative immunohistologic criteria are superior to the lymphocytic focus score criterion for the diagnosis of Sjögren's syndrome. Arthritis Rheum 1992;35(9):1075–87.
5. Lazarus MN, Isenberg DA. Development of additional autoimmune diseases in a population of patients with primary Sjögren's syndrome. Ann Rheum Dis 2005;64(7):1062–4.
6. McDonagh JE, Isenberg DA. Development of additional autoimmune diseases in a population of patients with systemic lupus erythematosus. Ann Rheum Dis 2000;59(3):230–2.

7. Chambers SA, Charman SC, Rahman A, et al. Development of additional autoimmune diseases in a multiethnic cohort of patients with systemic lupus erythematosus with reference to damage and mortality. Ann Rheum Dis 2007;66(9):1173–7.
8. Al Attia HM, Dabbash AK, Khadim RA. Associated autoimmune disorders in patients with classic lupus erythematosus. J Clin Rheumatol 2005;11(1):63–4.
9. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61(6):554–8.
10. Theander E, Manthorpe R. Developing radiological erosions in inflammatory connective tissue disease. Introducing: secondary erosive arthritis in primary Sjögren's syndrome. Hygie 1999;108(1):48–50.
11. Salliot C, Mouthon L, Ardizzone M, et al. Sjögren's syndrome is associated with and not secondary to systemic sclerosis. Rheumatology 2007;46:321–6.
12. Szanto A, Szodoray P, Kiss E, et al. Clinical, serological, and genetic profiles of patients with associated Sjögren's syndrome and systemic lupus erythematosus. Hum Immunol 2006;67:924–30.
13. Manoussakis MN, Georgopoulou C, Zintzaras E, et al. Sjögren's syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjögren's syndrome. Arthritis Rheum 2004;50(3): 882–91.
14. Bave U, Nordmark G, Lovgren T, et al. Activation of the type I interferon system in primary Sjögren's syndrome: a possible etiopathogenic mechanism. Arthritis Rheum 2005;52(4):1185–95.
15. Gottenberg JE, Cagnard N, Lucchesi C, et al. Activation of IFN pathways and plasmacytoid dendritic cell recruitment in target organs of primary Sjögren's syndrome. Proc Natl Acad Sci U S A 2006;103(8):2770–5.
16. Miceli-Richard C, Comets E, Loiseau P, et al. Association of an *IRF5* gene functional polymorphism with Sjögren's syndrome. Arthritis Rheum 2007;56(12): 3989–94.
17. Venables PJ. Sjögren's syndrome. Best Pract Res Clin Rheumatol 2004;18(3): 313–29.
18. Wielosz E, Majdan M, Zychowska I, et al. Coexistence of five autoimmune diseases: diagnostic and therapeutic difficulties. Rheumatol Int 2008;28(9): 919–23.
19. Ramos-Casals M, Nardi N, Brito-Zeron P, et al. Atypical autoantibodies in patients with primary Sjögren syndrome: clinical characteristics and follow-up of 82 cases. Semin Arthritis Rheum 2006;35(5):312–21.
20. Heaton J. Sjögren's syndrome and systemic lupus erythematosus. Br Med J 1959;1:466.
21. Pan HF, Ye DQ, Wang Q, et al. Clinical and laboratory profiles of systemic lupus erythematosus associated with Sjögren syndrome in China: a study of 542 patients. Clin Rheumatol 2008;27(3):339–43.
22. Rovensky J, Tuchynová A. Systemic lupus erythematosus in the elderly. Autoimmun Rev 2008;7(3):235–9.
23. Ramos-Casals M, Brito-Zeron P, Font J. The overlap of Sjögren's syndrome with other systemic autoimmune diseases. Semin Arthritis Rheum 2007;36(4):246–55.
24. Scofield RH, Bruner GR, Harley JB, et al. Autoimmune thyroid disease is associated with a diagnosis of secondary Sjögren's syndrome in familial systemic lupus. Ann Rheum Dis 2007;66(3):410–3.
25. Theander E, Jacobsson LTH. Features of systemic lupus erythematosus in patients with primary Sjögren's syndrome. A cross-sectional analysis of the 11 items

of the SLE criteria set and the levels of complement factors C3 and C4 in 100 primary Sjögren's syndrome patients. Lupus 2005;14(3):S231.
26. Gilboe IM, Kvien TK, Uhlig T, et al. Sicca symptoms and secondary Sjögren's syndrome in systemic lupus erythematosus: comparison with rheumatoid arthritis and correlation with disease variables. Ann Rheum Dis 2001;60:1103–9.
27. Rodnan G. The natural history of progressive sclerosis (diffuse sclerderma). Bull Rheum Dis 1963;1963(7):203–5.
28. Alarcon-Segovia D, Ibanez G, Hernandez-Ortiz J, et al. Sjögren's syndrome in progressive systemic sclerosis (scleroderma). Am J Med 1974;57:78–85.
29. Avouac J, Sordet C, Depinay C, et al. Systemic sclerosis-associated Sjögren's syndrome and relationship to the limited cutaneous subtype. Arthritis Rheum 2006;54(7):2243–9.
30. Salliot C, Gottenberg J, Bengoufa D, et al. Anticentromere antibodies identify patients with Sjögren's syndrome and autoimmune overlap syndrome. J Rheumatol 2007;34:2253–8.
31. Lindvall B, Bengtsson A, Ernerudh J, et al. Subclinical myositis is common in primary Sjögren's syndrome and is not related to muscle pain. J Rheumatol 2002; 29(4):717–25.
32. Kanellopoulos P, Baltoyiannis C, Tzioufas AG. Primary Sjögren's syndrome associated with inclusion body myositis. Rheumatology (Oxford) 2002;41(4):440–4.
33. Derk CT, Vivino FB, Kenyon L, et al. Inclusion body myositis in connective tissue disorders: case report and review of the literature. Clin Rheumatol 2003;22(4-5): 324–8.
34. Lindgren S, Manthorpe R, Eriksson S. Autoimmune liver disease in patients with primary Sjögren's syndrome. J Hepatol 1994;20(3):354–8.
35. Manthorpe R, Oxholm P, Prause JU, et al. The Copenhagen criteria for Sjögren's syndrome. Scand J Rheumatol 1986;Suppl 61:19–21.
36. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Arthritis Rheum 1993;36:340–7.
37. Onji M, Nonaka T, Horiike N, et al. Present status of autoimmune hepatitis in Japan. Gastroenterol Jpn 1993;28(Suppl 4):134–8.
38. Matsumoto T, Morizane T, Aoki Y, et al. Autoimmune hepatitis in primary Sjögren's syndrome: pathological study of the livers and labial salivary glands in 17 patients with primary Sjögren's syndrome. Pathol Int 2005;55:70–6.
39. Montano-Loza A, Crispín-Acuna J, Remes-Troche J, et al. Abnormal hepatic biochemistry and clinical liver disease in patients with primary Sjögren's syndrome. Ann Hepatol 2007;6(3):150–5.
40. Biro E, Szekanecz Z, Czirjak L, et al. Association of systemic and thyroid autoimmune diseases. Clin Rheumatol 2006;25(2):240–5.
41. Tunc R, Gonen MS, Acbay O, et al. Autoimmune thyroiditis and anti-thyroid antibodies in primary Sjögren's syndrome: a case-control study. Ann Rheum Dis 2004;63(5):575–7.
42. Jonsson H, Nived O, Sturfelt G. Thyroid disorders in systemic lupus erythematosus are associated with secondary Sjögren's syndrome. Ann Rheum Dis 1987; 46(4):349.
43. Sjögren H. Zur Kenntnis der Keratokonjunktivitis sicca (Keratitis filiformis bei Hypofunktion der Tränendrüse). Acta Ophthalmol 1933;11:1–151.
44. Reader SR, Whyte HM, Elmes PC. Sjögren's disease and rheumatoid arthritis. Ann Rheum Dis 1951;10(3):288–97.

45. Uhlig T, Kvien TK, Jensen JL, et al. Sicca symptoms, saliva and tear production, and disease variables in 636 patients with rheumatoid arthritis. Ann Rheum Dis 1999;58(7):415–22.
46. Jacobsson L, Hansen BU, Manthorpe R, et al. Association of dry eyes and dry mouth with anti-Ro/SS-A and anti-La/SS-B autoantibodies in normal adults. Arthritis Rheum 1992;35(12):1492–501.
47. Hay EM, Thomas E, Pal P, et al. Weak association between subjective symptoms and objective testing for dry eyes and dry mouth: results from a population based study. Ann Rheum Dis 1998;57:20–4.
48. Young A, Koduri G. Extra-articular manifestations and complications of rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007;21(5):909–27.
49. Carmona L, Gonzalez-Alvaro I, Balsa A, et al. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis 2003;62(9):897–900.
50. Young A, Dixey J, Cox N, et al. How does functional disability in early rheumatoid arthritis affects patients in their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). Rheumatology 2000;39:603–11.
51. Skoumal M, Wottawa A. Long-term observation study of Austrian patients with rheumatoid arthritis. Acta Med Austriaca 2002;29(2):52–6.
52. Alexiou I, Germenis A, Koutroumpas A, et al. Anti-cyclic citrullinated peptide-2 (CCP2) autoantibodies and extra-articular manifestations in Greek patients with rheumatoid arthritis. Clin Rheumatol 2008;27(4):511–3.
53. Fujita M, Igarashi T, Kurai T, et al. Correlation between dry eye and rheumatoid arthritis activity. Am J Ophthalmol 2005;140(5):808–13.
54. Kauppi M, Pukkala E, Isomäki H. Elevated incidence of hematologic malignancies in patients with Sjögren's syndrome compared with patients with rheumatoid arthritis (Finland). Cancer Causes Control 1997;8:201–4.
55. Martens PB, Pillemer SR, Jacobsson LTH, et al. Survivorship in a population based cohort of patients with Sjögren's syndrome, 1976–1992. J Rheumatol 1999;26(6):1296–300.
56. Turesson C, O'Fallon WM, Crowson C, et al. Occurrence of extra-articular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol 2002;29:62–7.
57. Iltanen S, Collin P, Korpela M, et al. Celiac disease and markers of celiac disease latency in patients with primary Sjögren's syndrome. Am J Gastroenterol 1999; 94(4):1042–6.
58. Luft LM, Barr SG, Martin LO, et al. Autoantibodies to tissue transglutaminase in Sjögren's syndrome and related rheumatic diseases. J Rheumatol 2003;30(12):2613–9.
59. Roth EB, Theander E, Londos E, et al. Pathogenesis of autoimmune diseases: antibodies against transglutaminas, peptidylarginine deiminase and protein-bound citrulline in primary Sjögren's syndrome, multiple sclerosis and Alzheimer's disease. Scand J Immunol 2008;67(6):626–31.
60. Gurling KJ. Association of Sjögren's and Felty's syndromes. Ann Rheum Dis 1953; 12(3):212–6.
61. Lin LH, Tsai CN, Liu MF, et al. Common variable immunodeficiency mimicking rheumatoid arthritis with Sjögren's syndrome. J Microbiol Immunol Infect 2005; 38(5):358–60.
62. Hoppenreijs EP, van Dijken PJ, Kabel PJ, et al. Hereditary C1q deficiency and secondary Sjögren's syndrome. Ann Rheum Dis 2004;63(11):1524–5.
63. Ostrowski RA, Robinson JA. Antiphospholipid antibody syndrome and autoimmune diseases. Hematol Oncol Clin North Am 2008;22(1):53–65, vi.

Patient-Reported Outcomes Including Fatigue in Primary Sjögren's Syndrome

Simon J. Bowman, PhD, FRCP

KEYWORDS

• Sjögren's • Outcome • Fatigue • Clinical trials

The hallmark of Sjögren's syndrome is focal lymphocytic infiltration of exocrine glands leading to mucosal dryness, particularly of the eyes and mouth.[1] In addition, approximately 70% of patients report fatigue as a particularly prominent and disabling feature associated with reduced health-related quality of life.[2–4] Other key patient-reported extraglandular symptoms include arthralgia, myalgia, and Raynaud's phenomenon.[5–8]

This article reviews these patient-reported features, their relationships with objective assessment of the disease, potential therapies for these symptoms, and how measurements of these symptoms are relevant to outcome assessment in clinical therapeutic trials. While some of these features are also relevant to secondary Sjögren's syndrome, this article focuses on primary Sjögren's syndrome (PSS).

FATIGUE

Fatigue is also commonly reported by patients with other rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus.[2–4] Furthermore, fatigue is relatively common in the general population[9] and can present in association with certain medical conditions (eg, hypothyroidism), or with psychiatric diseases (eg depression), or be medically unexplained (eg, chronic fatigue syndrome).[9] One useful model, therefore, considers the interrelationships of biological (eg, ''disease activity,'' sleep), psychological (eg, depression and personality), and social factors (eg, family circumstances, life events).[10]

In terms of how ''disease activity'' or biological factors might contribute to fatigue in PSS, one approach is to look for associations between levels of fatigue and biological measures. A small number of studies have looked at such associations in PSS by examining correlations in cross-sectional studies between levels of fatigue and levels

Rheumatology Department, University Hospital Birmingham (Selly Oak), Birmingham B29 6JD, UK
E-mail address: simon.bowman@uhb.nhs.uk

Rheum Dis Clin N Am 34 (2008) 949–962
doi:10.1016/j.rdc.2008.08.010 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

of inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), antibodies (immunoglobulin levels, anti-Ro/La antibody titres), or cytokines, such as IL-1β, IL-2, IL-6, IL-10, and tumor necrosis factor α. These studies were unable to identify any associations.[3,11,12] My colleagues and I,[2] in our studies developing the Profile of Fatigue and Discomfort (PROFAD), a fatigue measure, have shown that the character or ''profile'' of fatigue among patients with PSS is very similar to that seen in patients with systemic lupus erythematosus. While this does not directly address the issue of biological versus psychosocial contributors to fatigue in PSS, it does suggest that, if fatigue in PSS has similar characteristics to those in systemic lupus erythematosus, it may share a similar aetiopathogenesis.

With regard to psychosocial factors, one study showed higher levels of depression in 62 PSS patients than in 38 rheumatoid arthritis patients or 63 healthy controls,[13] but the finding of identical mean depression scores for rheumatoid arthritis patients and healthy controls in this study differs from that for other studies, which have shown that patients with PSS have a similar prevalence of low mood to that found in other chronic rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus, and that there is a correlation between the low mood and some aspects of fatigue in PSS.[2,3,12]

Huyser and colleagues[14] found relatively weak associations between disease activity and fatigue in rheumatoid arthritis patients with the best predictors of fatigue being pain, depressive symptoms, and female sex. In our study to develop and validate a systemic disease activity score, the Sjögren's systemic Clinical Activity Index (SCAI),[5] we demonstrated correlations between fatigue, arthritis and Raynaud's domains of the SCAI and comparable domains of the PROFAD. The relationship, however, between ''fatigue'' and an overall measure to quantify the spectrum of systemic organ involvement, or a ''disease activity'' score, whether glandular or extraglandular, is likely to be more complex at least in part because of the nonbiological contributors to fatigue (including personality, low mood, and social factors).

Fibromyalgia appears to play only a minor role in PSS[15] and some data suggest that social factors also play a role in the levels of fatigue and other key symptoms in PSS.[16]

The effects of therapy on improving fatigue and what this might tell us about the extent to which fatigue reflects biological versus psychosocial factors in PSS are discussed further below.

MEASUREMENT OF FATIGUE AND OTHER EXTRAGLANDULAR SYMPTOMS

The simplest way of measuring fatigue (or indeed other symptoms, such as joint/muscle pain or Raynaud's) is to use a 10-cm visual analog scale (VAS) asking the patient to rate his or her fatigue (ie, from ''none'' at minimum to ''worst fatigue imaginable'' at most). Another approach is to use a questionnaire comprising a series of questions, each of which addresses some different component of the symptom under evaluation (**Table 1**). Some of these fatigue questionnaires eg, the Functional Assessment of Chronic Illness Therapy—Fatigue scale[17] and the Fatigue Severity Scale[18] are described as ''unidimensional.'' That is, they give a total score for fatigue much as the fatigue VAS does. Evidence from clinical trials in rheumatoid arthritis shows that a VAS may be just as effective as a longer questionnaire,[19] particularly in relation to sensitivity to change. Therapeutic studies in PSS may show similar results.[20] One might conclude, therefore, that a simple VAS is all that is needed as a primary outcome measure for the symptom of interest. Using even a simple, unidimensional, fatigue questionnaire in parallel with the VAS, however, offers reassurance that the VAS findings are valid and can, therefore, be a useful confirmatory secondary outcome tool.

Table 1
Fatigue scales

	Multidimensional Fatigue Inventory (MFI)	Revised Piper Fatigue Scale (PFS)	Fatigue Assessment Instrument (FAI) and Fatigue Severity Scale (FSS)	Chalder Fatigue Scale (CFS)	Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F)	Profile of Fatigue and Discomfort (PROFAD)
Number of questions	20	22	29 for FAI; 9 for FSS	14	13	19 for long form; 9 for short form
Subscales/ domains	General fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue	Behavioral/ severity, affective meaning, sensory, cognitive/ mood	FAI: global severity, situation-specific, consequences, response to rest/sleep; FSS: not applicable	Physical fatigue, mental fatigue	Not applicable	Physical fatigue, mental fatigue (plus arthralgia and "cold hands")
Designed for:	Cancer patients	Breast cancer	Multiple sclerosis and systemic lupus erythematosus	General practice	Cancer	Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus

Other questionnaires are ''multidimensional.'' That is, they have a series of domains or subscales that try to assess different aspects of fatigue.[2,21–24] In some of these questionnaires a total score can also be calculated. The individual questions that make up these questionnaires and the resulting domains offer a useful insight into what is meant by the term *fatigue*. One common theme is the differentiation between ''physical fatigue'' (eg, lack of energy, difficulty in getting started, easily worn out, feeling weak) and ''mental fatigue'' (eg, difficulty in concentrating or thinking). Although the exact phraseology differs among questionnaires, these two basic concepts are reflected in all five of the above multidimensional fatigue questionnaires. In addition, some questionnaires, such as the Fatigue Assessment Instrument[22] and Piper Fatigue Scale[23] explore other concepts, such as fatigue severity, the consequences of fatigue on daily activities, or the emotional consequences of fatigue.

In practical terms, however, such as the consideration of fatigue as a potential outcome in clinical trials,[25] as is discussed below, the predominant concepts are that of ''total'' or ''global'' fatigue measured either by the VAS or by questionnaires, and the domains of ''physical fatigue'' and ''mental fatigue,'' typically measured by multidimensional questionnaires. Another widely used questionnaire in rheumatology research is the Medical Outcomes Study Short-Form 36-item questionnaire (SF-36).[26] This eight-domain questionnaire includes a ''vitality'' domain, which generally correlates reasonably well with fatigue questionnaires.[2] Fatigue, however, is just one component of health-related quality of life and should not be equated as an identical concept.

Questionnaires for measuring fatigue (and other symptoms) are likely to generate similar results when measuring ''like to like,'' as in the case, for example, when using the Multidimensional Fatigue Inventory (MFI) and the PROFAD to measure physical fatigue or mental fatigue.[27] ''Fatigue'' in PSS–rheumatoid arthritis measured by VAS appears to correlate better with ''somatic fatigue'' domain scores of multidimensional fatigue questionnaires than with ''mental fatigue'' domain scores.[28,29] Therefore, apparently, patients with PSS or rheumatoid arthritis generally associate the term *fatigue* (eg, measured by the VAS) primarily with physical rather than mental fatigue.

To examine how best to measure fatigue as well as other symptoms in PSS, we started in 2000 by reviewing the literature and interviewing patients to get an idea of key disease symptoms. We then constructed and refined a symptom questionnaire, which was then completed by patients with PSS, rheumatoid arthritis, and systemic lupus erythematosus and by community controls without rheumatic disease. The questionnaire listed a wide range of symptoms, including constitutional, pulmonary, neurologic, urological, and other general and organ-specific symptoms of potential relevance to PSS. By eliminating symptoms that were either infrequent or common to the community control group (ie, not disease-specific), we produced the PROFAD, a profile that captured the symptomatic component of PSS.[2] The resulting measure comprised only a limited set of symptoms (ie, fatigue, joint and muscle pain) as well as a ''cold hands'' domain, which essentially reflected, at least in a United Kingdom cohort, Raynaud's phenomenon. The conclusion of this study is that these symptoms are the key extraglandular symptoms of PSS of relevance to clinical study outcome.

POTENTIAL APPROACHES TO TREATMENT OF FATIGUE AND OTHER EXTRAGLANDULAR SYMPTOMS

The most commonly used medication in our experience to treat fatigue and joint/muscle pain in PSS is hydroxychloroquine. Fox and colleagues[30] reported improvement in arthralgia and myalgia (five-point Likert scale) in an open-label retrospective study in

50 patients treated for a minimum of 2 years with hydroxychloroquine 6 to 7 mg/kg/d. Kruize and colleagues[31] in 2003 performed a small crossover study in 19 patients over 2 years (12 months on placebo or hydroxychloroquine 400 mg/d switched to the other for a second 12 months). They found no difference in the presence and severity in a number of symptomatic outcomes or glandular function compared with the previous visit, although hypergammaglobulinaemia improved. However, although many clinicians use hydroxychloroquine in clinical practice, there has never been an adequately powered double-blind randomized controlled clinical trial (RCT) of hydroxychloroquine in PSS and, therefore, its efficacy remains unproven in formal studies.

Infliximab, however, has been studied in an RCT in 103 patients with PSS.[32] The outcome chosen was an ad hoc composite of VASs of fatigue, pain, and dryness in which patients had to score greater than 50 mm on at least two of these at baseline and demonstrate a 30% improvement at 10 weeks compared with baseline for at least two of the three components. Unfortunately, the study was negative, both in terms of this composite outcome and in terms of each of the individual components.

Results from another double-blind RCT, this time of dehydroepiandrosterone (DHEA) 200 mg once a day versus placebo for 12 months in 60 patients with PSS, were reported recently by Hartkamp and colleagues[33] Patients in both active therapy and placebo groups showed improvement in primary outcomes of fatigue, mental well-being, and depressive mood but without any difference between active treatment and placebo. The belief of having used DHEA was a stronger predictor of improvement than whether DHEA was actually used or not. The conclusion was that if the placebo effect is so significant then cognitive behavioral therapies might have a role to play.

Taking a nonbiological therapeutic approach, Strombeck and colleagues[34] examined the effect of exercise on fatigue and aerobic exercise capacity in 9 patients with PSS over a 12-week period compared with 10 patients who did not pursue an exercise regime over this period. Both of these components, as well as depression, improved, although there was no relationship between the improvement in fatigue and improvement in aerobic capacity in individual patients. This study suggests that nonmedical approaches to treating fatigue may be successful.

However, pilot clinical data for anti-CD20 therapy (rituximab),[20,35–38] as well as data from an open-label study of anti-CD22 antibody (epratuzimab),[39] paint a different picture. In our study,[20] 17 patients with PSS and a score on fatigue VAS greater than 50 mm were randomized to receive either two infusions of rituximab 1g or placebo; patients also received oral and intravenous steroids. Outcome measures included (1) the proportion of patients with more than 20% reduction in fatigue VAS, (2) changes in PSS-related symptoms, (3) health-related quality of life, and (4) immunologic parameters of PSS. These were measured 6 months after therapy. Results demonstrated significant improvement from baseline in fatigue VAS in the rituximab group ($P < .001$) in contrast to the placebo group ($P = .147$), which became more apparent over time (**Fig. 1**). There was also a significant difference between the groups at 6 months in the social functioning score of SF-36 ($P = .01$) and a trend to significant difference in the mental health domain score of SF-36 ($P = .06$). There was one episode of serum sickness in the rituximab-treated group. This data and studies by other groups suggest potential benefit in treating fatigue,[20,35,38,39] dryness symptoms,[35,36] and systemic features.[37] If, therefore, fatigue improves following biologic therapy, one could argue that, in contradistinction to the above studies, this might suggest a biological mechanism for at least part of the fatigue symptoms in PSS.

The utility of fatigue and other patient-reported outcomes in clinical trials in rheumatoid arthritis has also been studied. Wells and colleagues[25] recently evaluated the relative responsiveness to anti–tumor necrosis factor therapy of disease activity

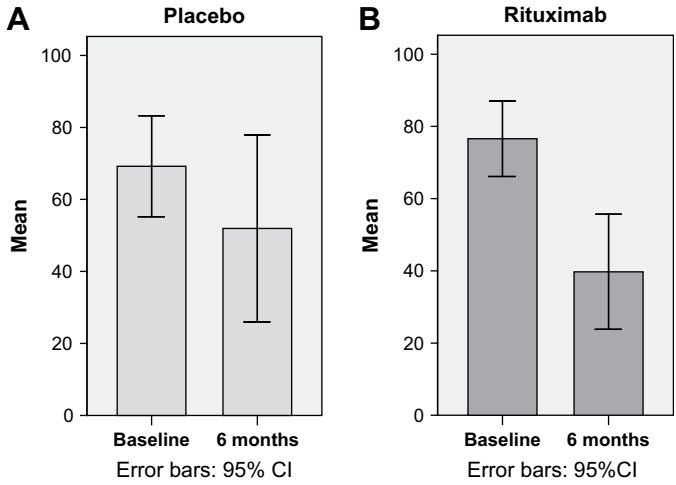

Fig. 1. (*A*) Mean fatigue VAS at baseline and 6 months. (*B*) Change in fatigue VAS from baseline. (*From* Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren's syndrome with rituximab: results of a randomised, double-blind, placebo controlled pilot study. Ann Rheum Dis 2008;67:1541–4; with permission.)

components (swollen and tender joint counts, patient and physician global assessments, erythrocyte sedimentation rate, C-reactive protein) with patient-reported outcomes (pain, fatigue, sleep, SF-36, and Health Assessment Questionnaire). Generally, the physician global assessment and the patent-reported SF-36 physical component score, pain outcomes, and fatigue outcomes were more reliable in detecting a treatment effect than the tender joint count, suggesting that these patient-reported outcomes are responsive to change following treatment and can be used as part of the outcome assessment process in rheumatoid arthritis. In an observational study by Wolfe and Michaud,[40] anti–tumor necrosis factor and other nonbiological disease-modifying antirheumatic drug therapies had the same level of beneficial effect on reducing fatigue. Changes in pain (VAS) and function (measured by the Health Assessment Questionnaire), however, correlated more strongly over a 6-month period with changes in patients' assessment of their health status ((±much) better/same/(±much) worse) than changes in fatigue levels.[40] These studies suggest that in rheumatoid arthritis, fatigue can be used as an outcome measure, but that other symptoms, such as joint pain and function, are more important than fatigue to rheumatoid arthritis patients, although, of course, the same may not be the case in PSS.

DRYNESS (SICCA) SYMPTOMS

Dryness is the key symptom of Sjögren's syndrome, with oral and ocular dryness as the most common and troublesome component.[1] As with fatigue, pain, or other extraglandular symptoms, the simplest way to measure dryness is with a VAS, but questionnaires can add detail and reliability. A number of dryness questionnaires have been developed. Many are screening questionnaires to identify the presence or absence of dryness symptoms in the community or as part of classification criteria for Sjögren's syndrome.[41,42] Some questionnaires have been developed to quantify oral (**Table 2**) [43–50] and ocular (**Table 3**) [49–52] dryness, although this list is not exclusive. As with fatigue questionnaires, some of these are unidimensional,[43,44,47] some are

Table 2
Oral dryness measures

	VAS	Fox et al[30]	Ship et al	Xerostomia-Related Quality of Life Scale	Oral Health Impact Profile	Xerostomia Inventory	Liverpool Sicca Inventory	Sicca Symptoms Index	Vivino et al[50] ad hoc Measure
Number of questions	0 (100-mm line)	4	8	15	49	11	28 (17 oral in 3 domains, 7 ocular and 4 on vaginal dryness	24 oral questions (long form); 5 (short form)	6 oral questions (mixture of VAS and 3-point scales)
Subscales/ domains	Not applicable	Not applicable	Not applicable	Physical, pain, personal, social	Functional limitation, physical pain, psychologic discomfort, physical disability, psychologic disability, social disability, handicap	Not applicable	Oral symptoms, symptom control, sensory domain, ocular domain, sexual function	1 oral domain in 5 facets: difficulty eating, dry throat, bad breath, wetting mouth, oral problems	Not applicable
Designed for:	Generic measure	Dry mouth	Healthy adults	Quality of life in oral cancer	Dental patients	Adults age 65 or older	Sjögren's syndrome	Sjögren's syndrome	RCT in Sjögren's syndrome of pilocarpine

Table 3
Ocular dryness measures

	VAS	Ocular Surface Disease Index	National Eye Institute—Visual Function 25-item Questionnaire	Sicca Symptoms Inventory	Vivino et al ad hoc Measure
Number of questions	0 (100-mm line)	12	25	15 ocular questions on long form; 3 on short form	16 ocular questions (mixture of VAS and 3-point scales)
Subscales/ Domains	Not applicable	Vision-related function, ocular symptoms, environmental triggers	General vision, ocular pain, near vision, distance vision, social functioning, mental functioning, role functioning, dependency, driving, peripheral vision	1 ocular domain in 3 facets: sore eyes, eye irritation, poor vision	Not applicable
Designed for:		Dry eye severity in RCTs	Patients with eye disease	Sjögren's syndrome clinical trials	RCT of pilocarpine in Sjögren's syndrome

multidimensional,[45,46,48,49,51,52] and some also include questions on vaginal, cutaneous, bronchial, or nasal dryness.

There have been relatively few studies directly comparing different sicca questionnaires. In our study developing the Sicca Symptoms Inventory,[49] we identified similarities between the Sicca Symptoms Inventory and the Xerostomia Inventory. The National Eye Institute Visual Function 25-item Questionnaire (NEI-VFQ-25) has also been shown to correlate with results using the Ocular Surface Disease Index.[52] It is likely, however, that as with the measurement of fatigue and pain, using a VAS of dryness as the primary outcome measure along with a dryness questionnaire as a confirmatory secondary outcome measure is the most logical approach. Complicating the issue is the task of choosing the VAS. If one is going to pick a single dryness VAS as a primary outcome measure, what should it be? Should it be global dryness, worst dryness, oral dryness, ocular dryness, or some composite of all of these? To some extent, the choice depends on the study medication. Oral dryness might be most appropriate to use for a therapy targeting the mouth, and eye dryness for therapy targeting the eyes. However, in the case of systemic therapy, such as rituximab, the process of choosing might be more complex.

There are also a number of other uncertainties, however, with regard to dryness assessment. The first is the relatively weak correlation between dryness symptoms and objective measures of lachrymal and salivary flow.[53] This poses a dilemma in a clinical trial context: Should the primary outcome be improvement in salivary/lachrymal flow, or improvement in symptoms, or both? Also, with a placebo group response rate for improvement in symptoms of approximately 30%,[20,50] what is the minimum clinically meaningful response in the active group that should be reflected in the definition of the primary outcome?

Also, salivary flow can be measured either as basal (unstimulated) flow or as stimulated (eg, in response to a sharp stimulus such as lemon drops or a pastille). It seems most likely that chronic oral dryness and mucosal damage results from low or absent basal flow and, consequently, medication that improved basal dryness would be most logical to use in the treatment of PSS. The corollary of this is that, ideally, improvement in basal unstimulated flow is the outcome measure of choice. Clearly, however, such medications as pilocarpine or cevimeline, which directly stimulate salivary flow (see below), will, by definition, lead to improvement in stimulated flow in any individual with residual gland activity capable of responding to it. Even if this medication does not increase basal flow, the argument would be that, if taken regularly, the increase in stimulated flow may, over time, substitute for the lack of basal flow, improve patient symptoms, and reduce the degree of oral mucosal changes that result from chronic oral dryness even if unstimulated flow is unchanged.

What is needed at this stage, to address these issues, are some phase II trials of effective therapy to evaluate different VASs and flow measurements assessing these different components of dryness. These trials would provide formal data to assess the sensitivity to change of different dryness measures in the context of a randomized clinical trial.

DATA FROM EXISTING CLINICAL STUDIES

The largest trial of therapy of oral and ocular dryness in Sjögren's syndrome was performed by Vivino and colleagues[50] in 1999. They studied 373 patients with primary or secondary Sjögren's syndrome randomized to placebo (n = 125) or 2.5 mg pilocarpine four times a day (n = 121) or 5 mg pilocarpine four times a day (n = 127) for 12 weeks. Pilocarpine is a muscarinic agonist that stimulates exocrine glands. Five milligrams of

pilocarpine was effective in stimulating salivary flow at the start and throughout the study. There was no change, however, in the degree of stimulation following 5-mg pilocarpine at the start and end of the study, or in the basal salivary flow. Nevertheless, from a symptomatic perspective, patients on the 5-mg four-times-a-day dose had a significantly higher likelihood of responding as assessed by symptomatic measures of global dryness of eyes and mouth and of multiple items measuring individual dryness symptoms.

Cevimeline is another muscarinic agonist licensed in the United States and Japan for the treatment of dryness in PSS. Two published RCTs in the United States,[54,55] one involving 75 patients and the other involving 197 patients, as well as other studies in Japan, demonstrated similar data to the above study of pilocarpine.

Interferon alpha lozenges have also been studied for improvement in salivary function. In an open-label study of 150 IU three times a day for 6 months in 60 Sjögren's syndrome patients, Shiozawa and colleagues[56] found that salivary flow and histologic features improved, but patient-related outcomes were not reported. In a combined report from two phase III double-blind randomized controlled studies by Cummins and colleagues[57] of 497 patients with PSS, improvement in unstimulated whole salivary flow and seven of eight symptoms of oral dryness were observed although the chosen primary end points of a response from both stimulated whole salivary flow and VAS of oral dryness did not show statistically significant improvement.

Topical cyclosporine emulsion has also been studied in two large studies of ocular dryness. In the smaller study reported by Stevenson and colleagues,[58] 129 patients with dry eyes were treated with cyclosporine eye drops for 12 weeks at doses between 0.05% and 0.4% and 33 patients with vehicle alone. In 90 patients with moderate to severe disease, the 0.1% dose was most consistent in improving some objective and some subjective end points and the 0.05% does was most consistent in improving patient symptoms, including the Ocular Surface Disease Index. In the larger study of 877 patients by Sall and colleagues,[59] Schirmer tear test with anesthetic and corneal staining at 6 months improved significantly more in the active treatment groups compared with placebo, whereas Schirmer test without anesthetic improved with both active drug and the placebo (vehicle alone). Similarly the Ocular Surface Disease Index scores improved from baseline but there was no statistically significant difference compared with vehicle alone, although other subjective measures (blurred vision, artificial tear usage, and physician global assessment) did show benefit from active drug. These studies suggest that both the vehicle and active drug have beneficial effects with some added benefit from the cyclosporine component.

SUMMARY: MEASUREMENT OF PATIENT-REPORTED OUTCOMES IN CLINICAL TRIALS

The work described here has identified dryness and fatigue as the key patient-reported outcomes in PSS (with joint pain and Raynaud's also being frequent). In expert panel discussions, fatigue was felt to be a particularly important outcome domain in its own right, in relation to patients' disease experience.[60,61] We have also shown that fatigue can improve following systemic therapy[20] and there is increasing interest in fatigue as a secondary outcome measure in rheumatoid arthritis.[25,40] Nevertheless, because fatigue has psychosocial as well as biological causes, there is reasonable hesitation to rely on it exclusively as a single primary outcome measure, particularly where biological therapy is being considered. Other approaches are to use fatigue as part of a composite symptomatic outcome measure (eg, with pain and dryness symptoms)[32] or to incorporate fatigue into, or alongside, a systemic activity

measure.[5,62] This may depend on the trial medication being tested, but composite outcome measures themselves also need validation before being used.

The main issue for oral and ocular dryness is: Which global patient VAS should be used as a primary outcome measure—oral, ocular, or global? This again might depend on the study medication: for topical cyclosporine, clearly ocular dryness would be used; and for a salivary stimulant, oral dryness; in other circumstances, either an overall dryness VAS or whichever of the two measures—oral or ocular—had the higher baseline score might be appropriate. Response to objective assessments has been patchy. Even directly stimulating drugs, such as pilocarpine or cevimeline, have failed to show consistent improvement in basal salivary flow over 6 months and it is probably unrealistic to expect a biologic agent indirectly targeting salivary flow through down-regulation of B-cells to have a measureable effect on this over a 6- to 12-month period of study. The downside of using symptoms alone, however, is the significant placebo effect, at least in short-term (6–12 month) studies, which makes it more difficult to detect a treatment effect.

Despite these limitations, our understanding of how to measure outcome in PSS clinical trials has greatly advanced over the past decade and puts us in a position where RCTs in PSS can be considered with much greater confidence. Clinical trials will foster the development of more robust outcome measures.

REFERENCES

1. Jonsson R, Bowman SJ, Gordon TP. Sjögren's syndrome. In: Koopman WJ, Moreland LW, editors. Arthritis and Allied Conditions. 15th edition. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 1681–705, Chapter 78.
2. Bowman SJ, Booth DA, Platts RG, UK Sjögren's Interest Group. Measurement of fatigue and discomfort in primary Sjögren's syndrome using a new questionnaire tool. Rheumatology 2004;43:758–64.
3. Barendregt PJ, Visser MR, Smets EM, et al. Fatigue in primary Sjögren's syndrome. Ann Rheum Dis 1998;57:291–5.
4. Strömbeck B, Ekdahl C, Manthorpe R, et al. Health-related quality of life in primary Sjögren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using SF-36. Scand J Rheumatol 2000;29:20–8.
5. Bowman SJ, Sutcliffe N, Isenberg DA, et al. Sjögren's Systemic Clinical Activity Index (SCAI): a systemic disease activity measure for use in clinical trials in primary Sjögren's syndrome. Rheumatology 2007;46(12):1845–51.
6. Skopouli FN, Dafni U, Ioannidis JPA. Clinical evolution and morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000;29:296–304.
7. Pertovaara M, Pukkala E, Laippala P, et al. A longitudinal cohort study of Finnish patients with primary Sjögren's syndrome: clinical, immunological, and epidemiological aspects. Ann Rheum Dis 2001;60:467–72.
8. Davidson BK, Kelly CA, Griffiths ID. Primary Sjögren's syndrome in the North East of England: a long-term follow-up study. Rheumatology 1999;38:245–53.
9. Bates DW, Schmitt W, Buchwald D, et al. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. Arch Intern Med 1993;153(24): 2759–65.
10. Wessely S, Hotopf M, Sharpe M. Chronic fatigue and its syndromes. Oxford: Oxford University Press; 1998.
11. Hartkamp A, Geenen R, Bijl M, et al. Serum cytokine levels related to multiple dimensions of fatigue in patients with primary Sjogren's syndrome. Ann Rheum Dis 2004;63:1335–7.

12. Bax HI, Vriesendorp TM, Kallenberg CGM, et al. Fatigue and immune activity in Sjogren's syndrome. Ann Rheum Dis 2002;61:284.
13. Valtysdottir ST, Gudbjornsson B, Lindqvist U, et al. Anxiety and depression in patients with primary Sjogren's syndrome. J Rheumatol 2000;27:165–9.
14. Huyser BA, Parker JC, Thoreson R, et al. Predictors of subjective fatigue among individuals with rheumatoid arthritis. Arthritis Rheum 1998;41(12):2230–7.
15. Giles I, Isenberg D. Fatigue in primary Sjögren's syndrome: Is there a link with the fibromyalgia syndrome? Ann Rheum Dis 2000;59(11):875–8.
16. Andersson SI, Manthorpe R, Theander E. Situational patterns in coping with primary Sjögren's syndrome. Psychol Health Med 2001;6(1):29–40.
17. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13:63–74.
18. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Arch Neurol 1989;46:1121–3.
19. Wolfe F. Fatigue assessments in rheumatoid arthritis: comparative performance of visual analogue scales and longer fatigue questionnaires in 7760 patients. J Rheumatol 2004;31:1896–902.
20. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren's syndrome with rituximab: results of a randomised, double-blind, placebo controlled pilot study. Ann Rheum Dis 2008; [Epub ahead of print].
21. Smets EM, Garssen B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315–25.
22. Schwartz JE, Jandorf L, Krupp LB. The measurement of fatigue: a new instrument. J Psychosom Res 1993;37:753–62.
23. Piper BF, Dibble SL, Dodd MJ, et al. The revised Piper fatigue scale: psychometric evaluation in women with breast cancer. Oncol Nurs Forum 1998;25(4): 677–84.
24. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. J Psychosom Res 1993;37:147–53.
25. Wells G, Li T, Maxwell L, et al. Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis. Ann Rheum Dis 2008;67:260–5.
26. Ware JE, Snow KK, Kosinski M, et al. SF-36 Health Survey. Manual and interpretation guide. Boston: The Health Institute, New England Medical Center; 1993.
27. Goodchild CE, Treharne GJ, Booth DA, et al. Measuring fatigue among women with Sjögren's syndrome or rheumatoid arthritis: a comparison of the Profile of Fatigue (ProF) and the Multidimensional Fatigue Inventory (MFI). Musculoskeletal Care Dec 17, 2007 [Epub ahead of print].
28. Lwin-T CT, Bishay M, Platts RG, et al. The assessment of fatigue in primary Sjögren's syndrome. Scand J Rheumatol 2003;32:1–5.
29. Strombeck B, Theander E, Jacobsson LT. Assessment of fatigue in primary Sjogren's syndrome: the Swedish version of the profile of fatigue. Scand J Rheumatol 2005;34:455–9.
30. Fox RI, Dixon R, Guarrasi V, et al. Treatment of primary Sjogren's syndrome with hydroxychloroquine: a retrospective, open-label study. Lupus 1996;5(Suppl 1): S31–6.
31. Kruize AA, Hene RJ, Kallenberg CG, et al. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. Ann Rheum Dis 1993;52:360–4.

32. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome. Arthritis Rheum 2004;50:1270–6.
33. Hartkamp A, Geenen R, Godaert GL, et al. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren's syndrome: a randomised controlled trial. Ann Rheum Dis 2008;67(1):91–7.
34. Strombeck BE, Theander E, Jacobsson LTH. Effects of exercise on aerobic capacity and fatigue in women with primary Sjögren's syndrome. Rheumatology 2007;46:868–71.
35. Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjogren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Care Res 2007;57: 310–7.
36. Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum 2005; 52:2740–50.
37. Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann Rheum Dis 2007;66:351–7.
38. Levesque MC, Prak NL, St Clair EW, et al. Longitudinal analysis of lymphocyte subsets in patients with primary Sjogren's syndrome (pSS) treated with rituximab: results from an open-label clinical trial. Arthritis Rheum 2007;56(9 Suppl):S445.
39. Steinfeld SD, Tant L, Burmester G, et al. Epratuzimab (humanised anti-CD22 antibody) in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 2006;65:796–803.
40. Wolfe F, Michaud K. Fatigue, rheumatoid arthritis, anti-tumour necrosis factor therapy: an investigation in 24,831 patients. J Rheumatol 2004;31:2115–20.
41. McMonnies CW. Key questions in a dry eye history. J Am Optom Assoc 1986;57: 512–7.
42. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
43. Fox PC, Busch KA, Baum BJ. Subjective reports of xerostomia and objective measures of salivary gland performance. J Am Dent Assoc 1987;115:581–4.
44. Pai S, Ghezzi EM, Ship JA. Development of a visual analogue scale questionnaire for subjective assessment of salivary dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:311–6.
45. Henson BS, Inglehart MR, Eisbruch A, et al. Preserved salivary output and xerostomia-related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. Oral Oncol 2001;37:84–93.
46. Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. Community Dent Health 1994;11:3–11.
47. Thomson WM, Chalmers JM, Spencer AJ, et al. The Xerostomia Inventory: a multi-item approach to measuring dry mouth. Community Dent Health 1999;16:12–7.
48. Field EA, Rostron JL, Longman LP, et al. The development and initial validation of the Liverpool Sicca index to assess symptoms and dysfunction in patients with primary Sjogren's syndrome. J Oral Pathol Med 2003;32:154–62.
49. Bowman SJ, Booth DA, Platts RG, et al. UK Sjögren's Interest Group. Validation of the Sicca Symptoms Inventory (SSI) for clinical studies of Sjögren's syndrome. J Rheumatol 2003;30:1259–66.
50. Vivino FB, Al-Hashimi I, Khan Z, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren's syndrome. Arch Intern Med 1999;159:174–81.

51. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000;118:615–21.
52. Vitale S, Goodman LA, Reed GF, et al. Comparison of the NEI-VFQ and OSDI questionnaires in patients with Sjögren's syndrome-related dry eye. Health Qual Life Outcomes 2004;2:44.
53. Hay EM, Thomas E, Pal B, et al. Weak association between subjective symptoms of and objective testing for dry eyes and dry mouth: results from a population based study. Ann Rheum Dis 1998;57:20–4.
54. Fife RS, Chase WF, Dore RK, et al. Cevimeline for the treatment of xerostomia in patients with Sjögren's syndrome. A randomized trial. Arch Intern Med 2002;162: 1293–300.
55. Petrone D, Condemi JJ, Fife R, et al. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum 2002;46(3):748–54.
56. Shiozawa S, Tanaka Y, Shiozawa K. Single-blinded controlled trial of low-dose oral IFN-a for the treatment of xerostomia in patients with Sjogren's syndrome. J Interferon Cytokine Res 1998;18:255–62.
57. Cummins MJ, Papas A, Kammer GM, et al. Treatment of primary Sjogren's syndrome with low-dose human interferon α administered by the oromucosal route: combined phase III results. Arthritis Rheum 2003;49:585–93.
58. Stevenson D, Tauber J, Reis BL, The Cyclosporin A Phase 2 Study Group. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomised trial. Ophthalmology 2000;107:967–74.
59. Sall K, Stevenson OD, Mundorf TK, et al. CsA Phase 3 Study Group. Two multicenter, randomised studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. Ophthalmology 2000;107: 631–9.
60. Bowman S, Pillemer S, Jonsson R, et al. Revisiting Sjögren's syndrome in the new millennium: perspectives on assessment and outcome measures. Report of a workshop held on 23 March 2000 at Oxford, UK. Rheumatology 2001;40: 1180–8.
61. Pillemer SR, Smith J, Fox PC, et al. Outcome measures for Sjögren's syndrome, April 10–11, 2003, Bethesda, Maryland, U S A. J Rheumatol 2005;32:143–9.
62. Vitali C, Palombi G, Baldini C, et al. Sjögren's Syndrome Disease Damage Index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjögren's syndrome, derived from an analysis of a cohort of Italian patients. Arthritis Rheum 2007;56(7):2223–31.

Measurement of Disease Activity and Damage in Sjögren's Syndrome

Claudio Vitali, MD

KEYWORDS

• Sjögren's syndrome • Disease activity • Disease damage
• Outcome measures

The clinical course of systemic autoimmune diseases, including Sjögren's syndrome (SS), is commonly punctuated by episodes of varying duration in which the underlying immunologic mechanisms and the related inflammatory process become more evident.[1,2] From the clinical point of view, these flares are characterized by the appearance or worsening of signs and symptoms that are characteristic of each disease. Furthermore, in some of these diseases, phases of different disease activity are also accompanied by the elevation of acute phase reactants or by abnormalities of immunologic markers. If the disease process, once activated, does not spontaneously revert or remit as a consequence of adequate treatment, irreversible damage can be induced in the involved organs and systems.[1,2]

Aside from these general assumptions, the concepts of magnitude of disease activity and damage for different systemic autoimmune disorders are far from being exactly defined.[3] Conceptually, activity implies reversibility of the process and is usually characterized by inflammatory manifestations in various organs or systems. Damage represents the component of the disease process that is irreversible and can be defined as the presence of a permanent loss of function, or by radiographically or histologically evident structural derangement of the compromised organ or system.

Severity represents the cumulative effect of the reversible and irreversible pathologic abnormalities of the disease for a given individual. A disease manifestation, independent of the fact that it may be the expression of an active phase of the disease or the consequence of disease-related damage, is commonly considered severe when it can kill the patient, induce important disability, or is particularly resistant to treatment.

The author has worked as a consultant for GlaxoSmithKline, UK.
Department of Internal Medicine and Section of Rheumatology, 'Villamarina' Hospital, Piombino, Italy
E-mail address: c.vitali@yahoo.it

Rheum Dis Clin N Am 34 (2008) 963–971
doi:10.1016/j.rdc.2008.08.002 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

MEASUREMENT OF DISEASE ACTIVITY AND DAMAGE IN DIFFERENT SYSTEMIC AUTOIMMUNE DISEASES

Because specific clinical or biologic markers for the assessment of the degree of overall activity or cumulative damage in systemic autoimmune diseases do not exist, the measurement of these disease status entities can be facilitated by developing specific criteria for each disorder.[2–4] Such instruments are mainly designed to precisely assess activity or damage in patients enrolled in controlled therapeutic trials, but can also be used in daily clinical care.

Disease status criteria for activity and damage developed for these purposes should have, of course, the required clinometric and psychometric properties.[3,5] First, they should demonstrate their validity. Apart from the minimum requirement of face validity (which can be simply defined as measuring what they are designed to measure), they should consistently have construct and content validity. To have construct validity, the scoring algorithm should correlate with an independent measure of the state. In building disease status indices for autoimmune systemic diseases, the physician's global assessment (PGA) is commonly used as the external criterion that is then considered the gold standard. If this is valid, one can argue that the PGA effectively and simply accomplishes the purpose. However, data has shown that the PGA may be inaccurate,[6] particularly when given by differing observers with different cultural backgrounds and knowledge regarding a specific disorder.

In addition to having content validity, a clinical scale should cover all the relevant possible variables in the clinical expression of the disease. Reliability is another essential property for instruments devoted to measuring different clinical status entities. Generally speaking, reliability can be defined as the random error of a measurement system. If this error is in fact small, the measure can be considered reliable. Thus, reliability of a clinical scale can be optimized, elevating the standard of data collection and strictly defining the rules for data recording. Once data collection and compilation have been correctly accomplished, inter-observer reliability (stability of the measure when used by different operators) and intra-rater reliability (stability of the scale when used by the same operator on different occasions) can be more easily verified.

Finally, disease status criteria, and particularly those devoted to measuring a reversible entity, as disease activity, should demonstrate their sensitivity to any change in the clinical course, or at least to be able to appreciate important clinical differences in patients' status.[6,7] For this purpose, the concepts of minimal significant change and response criteria have been precisely defined for the most widely used activity criteria for autoimmune systemic diseases.

During the past 30 years, several activity criteria have been developed for the majority of the systemic autoimmune diseases.[4] While a plethora of activity criteria have been proposed for systemic lupus erythematosus,[5] a more restricted number has been validated and recommended for use in clinical and therapeutic trials and in daily practice.[8]

Instruments that can measure the degree of activity have also been proposed and validated for rheumatoid arthritis and are currently in use to assess the level of activity and variation of activity overtime for therapeutic trials and clinical practice.[4,7] More recently, a European consensus study group has developed and validated an activity criteria set for systemic sclerosis.[9]

A more restricted number of instruments are available to measure cumulative disease damage. A scoring system to assess the degree of damage in systemic lupus has been produced by an ad hoc committee of the American College of

Rheumatology,[10] while the articular damage in rheumatoid arthritis is commonly measured by standardized radiographic evaluation methods.[11]

METHODOLOGY UTILIZED TO DEVELOP DISEASE STATUS CRITERIA

Any scale that is aimed toward quantifying a global clinical assessment, as is the case of autoimmune systemic diseases, is a simplification of a complex intellectual process. An expert clinician is able to integrate a large amount of the patient's physical, biologic, and imaging-related findings, and reduce them to a more manageable size. This is accomplished by extrapolating only the relevant data, and excluding those of limited importance and those potentially influenced by other concomitant physiologic perturbations or related to other etiologies. The most commonly used approaches for selecting items for a clinical scale are by consensus or by applying statistical procedures.[3] In the consensus (Delphi) method, variables which may predict a disease status are preliminarily chosen by an expert committee. The derived scale is then tested for its construct and content validity in a group of true or simulated patients. Validation of the index and stratification of the included items for severity are finally obtained by applying the constructed scale to another series of patients. In certain cases, the PGA is used as an external criterion. Conversely, the selection of variables to be included in the scale can be obtained *ab initio* by analyzing a sufficiently large series of real patients and building a statistical multivariate model in which the items potentially useful to define a disease status entity are selected. In this case, the PGA represents the dependent variable of the multivariate model. This approach incorporates the construct validity and allows for stratification of the derived severity index by taking into account the weight of the different variables in the model. It does not, however, assure content validity when all of the possible, although rare, manifestations of the disease are not represented by the series of patients evaluated. Validation of the preliminarily constructed index should be performed at a later stage by application to a different series of patients.

PECULIARITIES OF THE CLINICAL SPECTRUM OF SS

Primary SS is a systemic autoimmune disease that mainly affects the exocrine glands and commonly presents as persistent dryness of the mouth and eyes because of functional impairment of the salivary and lachrymal glands. However, other epithelial organs may be involved, including liver, lung, and kidney. The histologic hallmark of SS is lymphocytic infiltration of the involved tissues (exocrine and nonexocrine epithelia). In early lesions the inflammatory infiltrates are mainly comprised of activated T cells, while in more advanced lesions B cells are predominant. In some tissues, and in particular phases of the disease, T- and B-lymphocytes form pseudofollicular structures surrounding the target epithelial chronic cells. Persistent B-cell activation and proliferation is considered to be another important feature of the disease.[12] Autoantibody production and hypergammaglobulinemia represent the serologic counterpart of this phenomenon, while cutaneous vasculitis, glomerulonephritis, and peripheral or central nervous system involvement are the related clinical manifestations.[13] B-cell activation and proliferation may sometimes evolve from a benign phenomenon to the development of different forms of B-cell lymphoma (see the article describing MALT lymphoma in SS elsewhere in this issue). The presence of hypocomplementemia, type II cryoglobulins, cutaneous vasculitis, and persistent parotid gland enlargement seems to be predictive for the development of malignant lymphoproliferation and consequently a worse disease prognosis.[14]

The clinical course of SS is relatively stable and benign in a majority of patients, and is largely characterized by sicca symptoms, fatigue, arthralgias, and myalgias. Sometimes, slowly progressive involvement of other epithelial tissues (quite frequently those of the upper airways, more rarely those of renal tubuli and the gastrointestinal tract) occurs. In about 20% of patients, more or less severe extraglandular systemic features dominate the clinical picture. Most frequent are Raynaud's phenomenon, arthritis, vasculitis leukopenia, and peripheral neuropathy. Glomerulonephritis and central nervous system manifestations are more rarely recorded.

At present there is no treatment capable of modifying the natural course of the disease and the therapeutic approach is based on symptomatic replacement or stimulation of glandular secretions, using tear and saliva substitutes and muscarinic agents. Extraglandular features are empirically treated with corticosteroids and immunosuppressive agents in a similar manner to what is commonly done for similar clinical manifestations in lupus patients. The availability of new biological agents that are potentially able to target molecules and receptors that appear to play a relevant role in the etiopathogenesis of SS may herald a new era in the management of patients with this disease.[15]

Although the first results obtained by the use of anti-tumor necrosis factor (TNF)-α agents were not very encouraging, some pilot studies in limited cohorts of patients have shown the potential utility of agents capable of modulating or blocking B-cell expansion and activity.[16,17] Because B-cell hyperactivation in SS could be the biologic counterpart of extraglandular manifestations, production of autoantibodies, immune-complexes, and complement consumption, patients with these particular clinical and serologic features appear to be the prime candidates for treatment with anti-B cell agents. Anti-CD20 monoclonal antibodies, which have shown some utility in open-label pilot studies,[17] are undoubtedly potentially useful agents to be tested in controlled trials on a multicenter basis. Because of the well-demonstrated importance of B-cell activation factor (BAFF; a recently described member of the TNF-ligand family) in controlling the B-cell maturation and survival in autoimmune systemic diseases,[18] BAFF-blocking agents may be promising therapies for those patients with SS who demonstrate clinical and serologic findings of B-cell activation.[16]

Whatever new therapeutic approaches warrant testing in patients with SS, some critical points remain to be defined. First, strict criteria should be preliminarily defined for the selection of patients to be included in specific trials. Different subsets of patients can be carefully identified from large cohorts, creating homogeneous subpopulations with well-defined clinical and biologic characteristics that may allow them to be considered as candidates for specific therapies targeting precise biologic processes. Second, investigators must ensure that each clinical trial uses accurately predefined end-points that are assessed with reliable and validated outcome measures. While a large number of clinical status indicators already exist and are widely used in therapeutic trials for rheumatoid arthritis and systemic lupus,[4] so far no validated instruments have been developed for SS. Nonetheless, progress has been made over the last several years in the development of damage and activity measures for primary SS. These will assist investigators in the assessment of the expanded available therapeutic armamentarium for SS.

THE ITALIAN EXPERIENCE

An effort was first made by an Italian group to define activity and damage criteria for SS.[19] To accomplish this, the method used to develop ECLAM (European Consensus Lupus Activity Measurement) was applied.[20] Data was collected on a total of 206 patients recruited in 12 Italian centers. This data was used to build two multivariate

models predictive of disease activity and damage, respectively. The PGA, recorded by observers for both activity and damage, represented the dependent variables for these two multivariate linear models. The variables included in these models were then used to define two clinical indices for damage (SSDDI or the SS Disease Damage Index) and for activity (SSDAI, or the SS Disease Activity Index) (**Table 1**). The weight of any variable included in each scale was derived from the coefficient that the variable demonstrated in the corresponding model. Patients who demonstrated a significant level of activity at the first observation time had data collected during a second clinical observation stage 3 months later. This was done to assess the variation of the level of disease activity over time and to test the capacity of SSDAI to appreciate changes of activity during the disease course (sensitivity to change).

In its final version, the SSDDI scale included 6 domains and 15 items, while 8 domains and 15 items were listed in the SSDAI. The strength of correlation between the SSDDI and SSDAI-recomputed scores and the respective PGA-based scores, preliminarily assigned for both damage and activity, was considered as a measure of the construct validity of both indices. The correspondence of scores assigned by the observers for the two clinical status entities was considered a measure of the construct validity for both indices. Sensitivity to change of SSDAI was also assessed by measuring the convergence between the time variation of the scores given by the observers over time and that of the scores recalculated by applying the constructed index.

Both SSDDI and SSDAI demonstrated construct validity. SSDAI also seemed to be rather sensitive to change. Because these indices were built from a rather limited series of patients and not developed in a multinational study, doubts could be raised regarding their content validity. The wide spectrum of SS manifestations could not be completely represented by a cohort of patients recruited in such a limited geographic area. Therefore, validity, particularly content validity, and reliability of SSDDI and SSDAI need to be verified in larger studies performed on different multinational cohorts.

THE BRITISH EXPERIENCE

Contemporaneous with the Italian group, a British group initiated the development and validation of an activity index to assess systemic features of SS,[21] based on a modified version of the previously developed BILAG (British Island Lupus Activity Group) index for systemic lupus.[22] BILAG is a multidimensional nominal scale that includes eight domains that are scored separately according to changes that have occurred since the previous observation. The stratification of the domains included in the scale is performed according the rater's intention to treat. The BILAG-derived Sjögren's Systemic Activity Index (SCAI) is constituted by a nine-domain structure. A factor analysis of the correlation matrix has shown the presence of a number of intercorrelated variables. This may reduce this instrument to a six-factor model. Construct validity of SCAI was also proved by measuring the correlation of this scale with the PGA, while its sensitivity to change was tested by comparing SCAI-derived flares to physician-defined disease flares. Similar to the SSDAI, SCAI has been constructed from a limited cohort of patients not collected on a multinational basis. Larger studies are certainly needed to definitely assess the validity and sensitivity to change of this scale.

A modified version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI)[10] has been tested on a relatively small number of lupus patients with secondary SS and patients with primary SS, and has proved to be a rather valid tool to measure certain domains of disease damage related to sicca complaints.[23] A further modified version of

Table 1
Sjögren's syndrome disease damage index

Variable	Definition	Score
Oral/salivary damage		
Salivary flow impairment	UWSC < 1.5 mL/15 min, by standard method	1
Loss of teeth	Complete or almost complete	1
Ocular damage		
Tear flow impairment	Schirmer's-I test < 5 mm/5 min, by standard method	1
Structural abnormalities	Corneal ulcers, cataract, chronic blepharitis	1
Neurologic damage		
CNS involvement	Long lasting stable CNS involvement	2
Peripheral neuropathy	Long lasting stable peripheral nerve or autonomic system impairment	1
Pleural-pulmonary damage	Any of the following:	2
	-Pleural fibrosis (confirmed by imaging)	
	-Interstitial fibrosis (confirmed by imaging)	
	-Significant irreversible functional damage (by spirometry)	
Renal impairment	Any of the following:	2
	-Stably raised serum creatinin or reduced GFR	
	-Tubular acidosis (urinary pH > 6 and serum bicarbonate< 15 mmol/L in two consecutive tests)	
	-Nephrocalcinosis (confirmed by imaging)	
Lymphoproliferative disease	Any of the following (clinically and histologically confirmed):	5
	-B cell lymphoma	
	-Multiple myeloma	
	-Waldenstrom's macroglobulinaemia	

Sjögren's Syndrome Disease Activity Index (SSDAI)

Item	Definition	Score
1. Constitutional complaints		
a. Fever	$\geq$38°C, not due to infections	1
b. Fatigue	Sufficiently severe to affect normal activities	1
c Δ of fatigue	New appearance or worsening of fatigue	1
2. Glandular complaints		
Δ of salivary gland swelling	New appearance or increasing swelling of major salivary glands (not due to infection or stones)	3
1. Articular complaints	Any of the following:	2
a. Artrhitis	Inflammatory joint pain in one or more joints[a]	
b. Evolving arthralgias	New appearance or worsening of joint pain without signs of articular inflammation[a]	

(*continued on next page*)

Table 1
(*continued*)

Item	Definition	Score
4. Hematological features		
a. Leuko/lymphopenia	<3500 / <1000 cmm	1
b. Lymphnode/spleen enlargement	Clinically palpable lymphnode/spleen	2
5. Pleural-pulmonary complaints	Any of the following:	4
a. Pleurisy	Confirmed by imaging, not due to infection	
b. Pneumonia (segmental or interstitial)	Ground glass aspects on CT scan, not due to infection	
6. Vasculitis		
Δ of vasculitis	New appearance or worsening or recurrent flares of palpable purpura	
7. Active renal involvement	Any of the following:	2
a. New or worsening proteinuria	More than 0.5 gr/day	
b. Increasing serum creatinine	Above the normal limits	
c. New or worsening nephritis	Glomerular or interstitial, histologically defined	
8. Peripheral neuropathy	Recent onset (< 6 months), proven by nerve conduction studies	1

Abbreviations: CNS, central nervous system; GFR, glomerular filtration rate; UWSC, unstimulated whole saliva collection.

[a] With exclusion of other causes of joint or muscle pain, lsuch as osteoarthritis, fibromyalgia, and so forth.

SLICC/ACR-DI for specific use in SS has been developed and refined by a British group comprised of specialists in the fields of rheumatology, ophthalmology, and oral medicine. Ocular and oral domains and eight systemic domains are included in a new SS damage index (SSDI).[24] Results of a longitudinal study, aimed at verifying the validity of this index in assessing cumulated damage of patients who have SS, have recently been published.[24]

THE EULAR INITIATIVE

Because national studies aimed at producing disease status criteria for SS may suffer from limitations, particularly in terms of content validity and amplitude of data collection, a multinational initiative sponsored by EULAR (European League Against Rheumatism) has recently begun. This is aimed at defining and validating a EULAR activity index for SS. A promoting committee, which includes investigators from 6 European countries and a large number of investigators from other European and overseas countries, has been constituted. These investigators have proven experience in the clinical management of patients with SS. The conceptual framework of the project begins with the consideration that the clinical spectrum of SS may vary from a relatively stable or slowly progressive disorder (commonly limited to exocrine gland involvement and accompanied by constitutional symptoms as fatigue and

pain because of musculoskeletal involvement) to a more aggressive and systemic disorder with a number of extraglandular features, usually accompanied by serologic signs of autoimmune activation. Thus, the task force of the project decided that at least two indices are needed. The first one should be able to assess sicca complaints and subjective symptoms, such as fatigue and pain; the second should be more oriented to assess global activity as expressed by the systemic features of the disease. Thus, two different arms of the study have been planned and are ongoing in parallel. Once both patient-reported and systemic activity indices are available, their validation in a second independent study will be required before use in therapeutic trials and daily clinical practice.

SUMMARY

SS is a systemic autoimmune disease that is characterized by an aggressive autoimmune response to epithelia, predominantly the salivary and lachrymal glands, with consequent reduction of their secretions accompanied by sicca complaints. Systemic features may also be present in a subset of patients and may require more aggressive therapies. Improvements in knowledge concerning disease pathophysiology, combined with the availability of specifically targeted therapies able to modulate or block some of the most important pathologic mechanisms of the disease, may open totally new perspectives in the therapeutic approach to SS. The absence of reliable and validated outcome measures for SS is a major obstacle in performing clinical trials of new therapies in SS. Studies devoted to defining outcome measurement instruments for this disorder have been performed or are in an advanced phases of completion.

REFERENCES

1. Symmonds DPM. Disease assessment indices: activity, damage and severity. Ballieres Clin Rheumatol 1995;9(2):267–85.
2. Fries JF, Hochberg MC, Medsger TA. Criteria for rheumatic diseases: different types and different functions. Arthritis Rheum 1994;37(4):454–62.
3. Liang MH. Translating outcomes measurement in experimental therapeutics of systemic rheumatic disease to patient care. Rheum Dis Clin North Am 2006; 32(1):1–8.
4. Pincus T, Sokka T. Complexities in the quantitative assessment of patients with rheumatic diseases in clinical trials and clinical care. Clin Exp Rheumatol 2005; 23(Suppl 39):S1–9.
5. Liang MH, Socher SA, Neal Roberts W, et al. Measurement of systemic lupus erythematosus activity in clinical research. Arthritis Rheum 1988;31(7):817–25.
6. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria. The American College of Rheumatology response criteria for systemic lupus erythematosus clinical trials: measures of overall disease activity. Arthritis Rheum 2004;50(11):3418–26.
7. Pincus T, Sokka T. Quantitative measures for assessing rheumatoid arthritis in clinical trials and clinical care. Best Pract Res Clin Rheumatol 2003;17(5):753–81.
8. Strand V, Gladman D, Isenberg D, et al. Outcome measures to be used in clinical trials in systemic lupus erythematosus. J Rheumatol 1999;26(2):490–7.
9. Valentini G, Della Rossa A, Bombardieri S, et al. European multicentre study to define disease activity criteria for systemic sclerosis. II. Identification of disease activity variables and development of preliminary activity indexes. Ann Rheum Dis 2001;60(6):592–8.

10. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39(3):363–9.
11. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27(1):261–3.
12. Mitsias DI, Kapsogeorgou EK, Moutsopoulos HM. Sjögren's syndrome: why autoimmune epithelitis? Oral Dis 2006;12(6):523–32.
13. Garcia-Carrasco M, Ramos Casals M, Rasas J, et al. Primary Sjögren's syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 2002;81(4):270–80.
14. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long term risk of mortality and lymphoproliferative diseases and predictive classification of primary Sjögren's syndrome. Arthritis Rheum 2002;46(3):741–7.
15. Ramos-Casals M, Brito-Zeron P. Emerging biological therapies in primary Sjögren's syndrome. Rheumatology (Oxford) 2007;46(9):1389–96.
16. Looney RJ. Will targeting B cells be the answer for Sjögren's syndrome? Arthritis Rheum 2007;56(5):1371–7.
17. Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann Rheum Dis 2007;66(3):351–7.
18. Szororay P, Jonnson R. The BAFF/APRIL system in systemic autoimmune diseases with special emphasis on Sjögren's syndrome. Scand J Immunol 2005; 62(5):421–8.
19. Vitali C, Palombi G, Baldini C, et al. Sjögren's syndrome disease damage index and disease activity index. Scoring systems for the assessment of disease damage and disease activity in Sjögren's syndrome, derived from an analysis of a cohort of Italian patients. Arthritis Rheum 2007;56(7):2223–31.
20. Vitali C, Bencivelli W, Isenberg DA, et al. Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. II Identification of the variables indicative of disease activity and their use in the development of an activity score. Clin Exp rheumatol 1992;10(5):541–7.
21. Bowman SJ, Sutcliffe N, Isenberg DA, et al. Sjögren's Syndrome Clinical Activity Index (SCAI)—a systemic disease activity measure for use in clinical trials in primary Sjögren's syndrome. Rheumatology (Oxford) 2007;46(12):1845–51.
22. Hay EM, Bacon PA, Gordon C, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Q J Med 1993;86(7):447–58.
23. Sutcliffe N, Stoll T, Pyke S, et al. Functional disability and end organ damage in patients with systemic lupus erythematosus (SLE), SLE and Sjögren's syndrome (SS), and primary SS. J Rheumatol 1998;25(1):63–8.
24. Barry RJ, Sutcliffe N, Isenberg DA, et al. The Sjögren's syndrome Damage Index (SSDI)—a damage index for use in clinical trials and observational studies in primary Sjögren's syndrome. Rheumatology 2008;47(8):1193–8.

Role of Nuclear Scintigraphy in the Characterization and Management of the Salivary Component of Sjögren's Syndrome

Frederick B. Vivino, MD[a,*], George A. Hermann, MD[b]

KEYWORDS

• Sjögren's syndrome • Salivary radionuclide scintigraphy

The revised rules of classification for both primary and secondary Sjögren's syndrome (SS) adopted by the American-European Consensus Group include the presence of objective salivary gland involvement defined by either unstimulated whole salivary flow of less than or equal to 1.5 mL/15 minutes, diffuse sialectasias by parotid sialography, or salivary scintigraphy showing ''delayed uptake, reduced concentration and/or delayed excretion of tracer.''[1] In this six-component schema, only histopathologic or serologic positivity is necessary (although not individually sufficient) for diagnosing primary SS. Although salivary scintigraphy may provide valuable and occasionally unique objective information about the major salivary glands, it, along with ocular and oral signs and symptoms, occupies a secondary hierarchal status and, as all imaging modalities, has not as been designated a valid outcome predictor of SS.[2,3] The current availability of electrostimulants, muscarinic agonists, and immune system modulators such as corticosteroids, cyclosporin, interferon-*a*, mizoribine, and antilymphocyte agents has engendered clinical trials that require standardized measures of prognosis and prediction of general SS therapeutic outcomes.[4–10] Within this context, when deciding which patients might be candidates for inclusion in various outcome trials, scintigraphy's ability to set apart processes caused by parenchymal

[a] Penn Presbyterian Medical Center, Penn Sjögren's Syndrome Center, University of Pennsylvania School of Medicine, 51 North 39th Street, 3910 Building, Philadelphia, PA 19104, USA
[b] University of Pennsylvania School of Medicine, Philadelphia, PA, USA
* Corresponding author.
E-mail address: frederick.vivino@uphs.upenn.edu (F.B. Vivino).

Rheum Dis Clin N Am 34 (2008) 973–986
doi:10.1016/j.rdc.2008.08.011 **rheumatic.theclinics.com**

damage or loss from those with cytokine/autoantibody-mediated, neuropathic, or other derangements may equal or exceed its contribution to the diagnosis of SS.

RADIONUCLIDE

For appraising deficits of salivary function associated with SS or radiation, ^{99m}Tc has remained the radionuclide of choice for 37 years, although recent interest has arisen in radiofluorodeoxyglucose positron emission tomography (PET).[11,12] Radiotechnetium is obtained by elution from a ^{99}Mo generator or "cow," whose predecessor is stable ^{98}Mo. Activation in a nuclear reactor yields ^{99}Mo that spontaneously decays with a half-life of 66 hours to ^{99m}Tc. ^{99m}Tc has a half-life of roughly 6 hours and is a pure 140 kEv gamma emitter. It is also inexpensive. This trio of properties makes it a nearly ideal imaging agent. The short physical half-life truncates its 3-day biologic half-life into an effective half-life of 6 hours. The gamma emission is contained easily by lead shielding and collimators but is sufficiently energetic to escape from the patient and interact efficiently with the NaI crystal detectors of the sensing camera. The lack of beta emission results in comparatively low total body radiation per dose, on the order of 3×10^{-7} Gy per MBq.[13] The gastrointestinal (GI) tract is the critical organ if the thyroid is blocked, receiving approximately 3.2×10^{-6} Gy per MBq.

Practical imaging of the salivary glands requires that radiopertechnetate be administered intravenously. Extrasalivary sites of its preferential localization include the choroid plexus, thyroid, gastric mucosa, sweat glands, and the lactating breast. Anionic pertechnetate enters the salivary acinar cells analogously to radioiodide, by means of the diuretic-sensitive $Na^+/K^+/Cl^-$ co-transport system, and it ultimately is partitioned between these cells and the striated ducts.[14] Whole-body elimination occurs by renal glomerular filtration and the GI tract.

Development of Salivary Scintigraphy

Taplin and colleagues[15] first imaged the major salivary glands in 1963 using radioiodine. One year later, Harper introduced the sodium pertechnetate salt of ^{99m}Tc into clinical imaging, and Bömer next visualized the glands using a rectilinear scanner.[16,17] Interest in salivary scintigraphy for diagnosing and evaluating patients who had SS arose with the work of Schall, who devised a categorical classification of parotid dysfunction.[18] Beginning in the 1970s, coupling of the Anger camera with digital computers spurred the growth of scintigraphy in general, with added capabilities of dynamic imaging, time–activity curves (TAC), wherein the radioactive count rate is plotted against time, and visual and numeric data manipulation. With these new capacities came new interpretive approaches that supplemented visual inspection. TACs appeared in 1972, percent of injected dose and stimulated excretion fraction in 1976, and glandular target-to-nontarget ratios in 1977.[19–21] TACs provided the raw data from which several indices, including the stimulated excretion fraction, were derived. The latter, analogous to a cardiac ejection fraction, is calculated from the formula: $(1-[\text{net minimal postsialagogue counts})/(\text{net maximum presialagogue counts}]) \times 100$ and measures the percent of trapped saliva emptied into the oral cavity in response to a sialogogic stimulus (**Fig. 1**). Net counts are those remaining in the organ of interest, in this case the salivary glands, after subtraction of nonspecific background counts arising from the patient's body and the local environment.

By 1980 the floodgates had opened to a torrent of so-called quantitative indices purporting to encapsulate parenchymatous trapping and uptake, resting and stimulated excretory function, and combinations thereof. All currently compete in detecting, staging, managing, and predicting the course of SS.[22–25] Disturbances of salivary

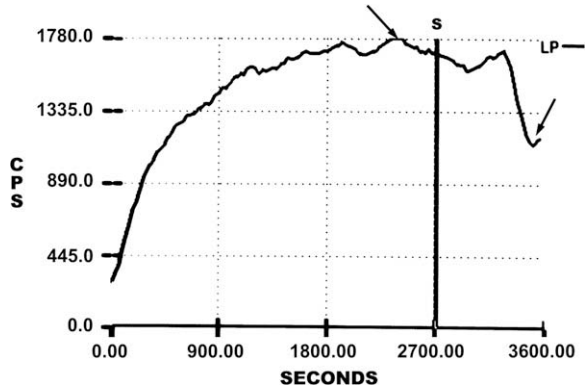

Fig. 1. Parotid time–activity curves used to compute the stimulated excretion fraction of the left parotid (LP) gland. Net maximum counts per second (CPS), indicated by the left arrow, are those attained within a 3-minute window preceding the sialogogic stimulus (S). Net minimal counts, indicated by the right arrow, are those attained at any time during the stimulation interval.

physiology, scintigraphically illuminated, became relevant to diagnosing and managing SS.

Protocols

Published scintigraphic protocols share a degree of commonality. Imaging the patient in the Waters projection provides a clear separation between the parotid and submandibular glands after the injection of radiopertechnetate (**Fig. 2**). Multiple sequential images are recorded and stored digitally. Late in the procedure, the patient receives a stimulant to induce glandular discharge. Upon review, sundry regions of interest are outlined from which to generate TACs. The patient often receives a small dose of oral potassium perchlorate at the study's conclusion to minimize thyroid and salivary gland radiation exposure.

Fig. 2. Patient imaged in Waters projection with the orbital–meatal line approximately at a 37° angle from the detector head plane. Neck is hyperextended slightly. Parotid and submandibular images are separated well.

Within these limits, depending on one's perspective, a splendid diversity or a chaotic lack of consistency marks reported practice. The gamma camera's detector usually is positioned anterior to the patient, but posterior, oblique, lateral, dual detector, and single photon emission tomograhic variants exist.[19,21,26–28] The administered dose of radiotracer may be fixed or adjusted according to patient weight and varies from 0.5 mCi to 15 mCi or 18.5 to 555 MBq.[19,29] Total study duration has ranged from 120 down to 5 minutes, although recent practice favors 60 minutes.[21,30] The duration of each image frame, inversely proportional to temporal resolution, varies from 300 to 5 seconds.[8,31] Monitoring of oral cavity activity may or may not occur.[32,33] Stimulants to induce salivary discharge are essential for calculation of the stimulated excretion fraction. They and their duration of action have enjoyed or suffered from similar inconstancy. Roughly one third of protocols published since 1969 rely on oral lemon juice. Ascorbic, citric, and tartaric acids appear less frequently.[34–36] Lemon candy and potassium perchlorate occasionally are encountered.[20,30] A sialogogue need not be oral. Workers have administered parenteral pilocarpine and carbechol.[8,37]

The wretched and painful oral hygiene often accompanying xerostomia is known. Early in the authors' clinical practice, it became obvious that the use of oral acids or lemon juice caused great patient discomfort, with which one could empathize readily after sampling these sialogogues incident to standardizing their own clinic's protocol. The authors switched to hard lemon candy, which was tolerated better and had additional advantages of easy administration and protracted stimulation. The authors now consider the former agents unsuitable for clinical practice. Nonoral stimulants offer an alternative, although uncertainties regarding optimal dose, differential effectiveness of oral versus parenteral administration, and untoward adverse effects remain unaddressed.[38]

Quantitative Indices

Diagnostic performance is highly process- and task-dependent. Once raw data have been gathered, the interpreter must choose which of an array of decision variables best depicts glandular uptake and excretory function. These include visual inspection of the ciné, TAC classification, and multiple so-called quantitative indices such as percent uptake of counts injected, gland-to-background ratio, uptake slope, time elapsed to peak counts, maximum-to-initial count ratio, gland-to-thyroid count ratio, and rapidity or magnitude of postsialogogue salivary excretion.[39–42]

In 1993, Kosuda, extending the work of Mita and Sugihara, employed a four-category classification based on visual inspection of uptake TACs whose progressive flattening correlated with increasing abnormality in labial salivary gland biopsy.[43,44] Visual inspection of TACs requires stratifying what is actually a continuous variable and faces pitfalls if ciné review is not performed. Curve configuration is not scale-invariant and is subject to misleading configuration when multiple TACs are plotted in the same graphic space. Normal submandibular and, with lesser prevalence, parotid glands punctuate uptake by periodic unstimulated excretion of saliva into the oral cavity.[29,31,35] It is the synchronous conflation of trapping, uptake, and unstimulated secretion that renders problematic any single quantitative index as a reliable descriptor of parenchymatous salivary status. This physiologic trait increases the scatter of many indices such as the apportioned percentage of parotid versus submandibular activity, the maximum ratio of late versus early counts, or its time of occurrence. Because normal controls and patients suffering from SS, chronic sialadenitis, drug-induced xerostomia, metabolic disorders, and radiation damage all show considerable scatter, most of these indices are poor performers.

Consequently, when attempting to discriminate among etiologic alternatives, salivary scintigraphy's diagnostic utility has been controversial.[9,45–47] Trapping and uptake of radiotracer are modified significantly by uncontrolled variables such as extraglandular, extrathyroidal volume of distribution, tracer washback into the vascular and interstitial compartments, body iodide or other competing ion load and thyrometabolic status, and hidden variables. Scott, working with a primate model, found that quantitative scintigraphy, expressed as percent uptake of administered tracer dose, was insensitive to glandular parenchymal loss of less than 25%.[48] Main duct ligation and atropine, however, precluded collection of secretory information.

Immune-mediated central and peripheral neurologic dysfunction accompanies SS and often impacts secretory behavior by autonomic derangement.[5,49,50] Therefore, it is not surprising that many workers have designated stimulated excretion a meaningful measure of this aspect of salivary function. The stimulated excretion fraction, alone or in combination with other parameters, appears to be the most frequently used quantitative index. Suggested reference ranges for the two sets of glands vary considerably, with those of the submandibulars consistently lower than those of parotid glands because of the former's more active unstimulated secretion that leaves less activity to be unloaded. Much variability likely derives from arbitrary background site selection, including brain, scalp, paraglandular, supraorbital, and neck.[7,20,22,24,39] Protocols subtracting a vascular-weighted template or even no background subtraction at all exist.[29,41] Insufficient background subtraction causes artifactual depression of calculated ranges, while too much subtraction errs in the opposite direction.

Enthusiasm for the excretion fraction is not universal. Receiver operating characteristic curve (ROC) analysis indicated that while this index could distinguish normal from SS reasonably well, it could not tell SS from chronic sialadenitis, radiation, or drug effects.[51] Nishiyama found that the parotid excretion fraction alone, when used to separate SS patients from controls, showed a sensitivity, specificity, and accuracy of 67%, 65%, and 66% respectively, mediocre performance.[52]

Interpretative attempts to capture trapping, uptake, and both phases of excretory function in a single quasi-quantitative expression started in 1971.[18] Initially, the constructs were frankly categorical classifiers. They grew increasingly multivariate, however. Current indices justifiably may be termed semiquantitative and describe the uptake and excretory status of each salivary gland that, when combined, render global salivary behavior in a single variable that may assume up to 28 differing values.[35,52] **Table 1** examines the diagnostic performance of four indices when presented with the least challenging of diagnostic tasks. Uptake ratio refers to the maximum count rate attained during the course of the study divided by the count rate at one minute. No significant difference in SS patient and control means is evidenced by the uptake ratio and the time it takes to peak. Although the stimulated excretion fraction and the

Table 1
Diagnostic performance of four quantitative indices in discriminating Sjögren's syndrome patients from controls

	Global Glandular Mean Index (± SE)			
	Stimulated Excretion Fraction	Time to Peak	Uptake Ratio	Functional Index
Controls (N=31)	80.6 (2.6)	8.3 (0.4)	6.5 (0.5)	8.5 (0.3)
Sjögren's (N=157)	52.4 (2.5)	7.9 (0.2)	6.1 (0.3)	16.8 (0.7)
p value	<0.001	0.4	0.6	<0.001

functional index show statistical significance, it fades as the diagnostic task becomes more arduous and more clinically realistic. Despite interest in univariant summation of salivary behavior, overlap among SS and non-SS populations remains a significant limitation to the utility of quantitative indices and their derivatives.

Those canons of diagnostic performance, sensitivity and specificity, have graced the salivary scintigraphic literature for 20 years. Both vary widely, sensitivity from 36% to greater than 95%, and specificity from 60% to 96%.[43,53–55] The authors' informal meta-analysis in 20 published studies containing explicit or derivable sensitivity reveals a mean of about 75%, and the mean specificity of 17 similar studies is 77%. Thus the mean false-positive rate is roughly 23% but, again, with broad range. These samples of course encompass a diverse group of test protocols, interpretative algorithms, patient populations, and diagnostic tasks.

Ironically, Blue's stimulated salivary clearance, a nonimaging procedure, is the only pertechnetate-based gauge that shows no overlap of SS sufferers (but not the radiated) and controls.[56] Demangeat revisited this work and correlated its results with several scintigraphic indices.[39] He found the best correlation with stimulated clearance was the early uptake slope between 1.5 and 4 minutes after injection. There was no correlation with the time to maximum activity and the stimulated excretion fraction. Because calculation of salivary clearance involves blood sampling and total saliva collection under continued gustatory stimulation by lemon juice, it is likely that scintigraphy will continue to be a routine vehicle of investigation.

Interpreting the Scintigram

It is not possible to describe current routine interpretative norms, because no international or national interlaboratory surveys have dealt with this issue. One then must choose an approach that might provide the most clinically helpful outcome. Review of the ciné sequence begins, and is essential for, interpretation. It is this act that permits selection of optimal frames from which to select the glandular and oral regions of interest that will be the sources of TACs. In doing so, the interpreter usually can get a general sense of the magnitude of individual glandular uptake and of excretion kinetics, and severity, pervasiveness, and distribution of dysfunction, if any. Interpretation involves discrimination of the functional gland from the dysfunctional, the normal from the abnormal. Published studies have offered control ranges, but the data are difficult to apply in daily clinical practice, lacking as they do standardized procedural guidelines.[27]

Normal salivary kinetics combines elements of early vascularity, trapping, uptake, unstimulated secretion mostly by the submandibular glands, and a response to gustatory or psychogenetic stimuli (**Fig. 3**). Derangement of one or more of these components in one or more glands signals an abnormality. The mildest deficit is loss of spontaneous parotid secretion, but this is difficult to detect because up to half of normal parotid glands secrete saliva in the resting state.[29,57] Therefore, perturbed nonstimulated parotid salivary flow likely exists among the xerostomic population but cannot be recognized in a given individual. In contrast, normal submandibular glands show almost universal cyclic resting secretion, absence of which constitutes objective evidence of dysfunction.[58] This might be categorized as a level 2 defect, level 1 being considered normal.

Level 3 defects involve loss of stimulated secretion alone and, although uncommon, may follow or supplant loss of resting discharge.[35] The stimulated ejection fraction, despite its limitations, probably represents the best single quantitative index to categorize discharge function, provided that attention is paid to what has occurred in the oral cavity before stimulation. Cutoff values range widely but average roughly 50%.

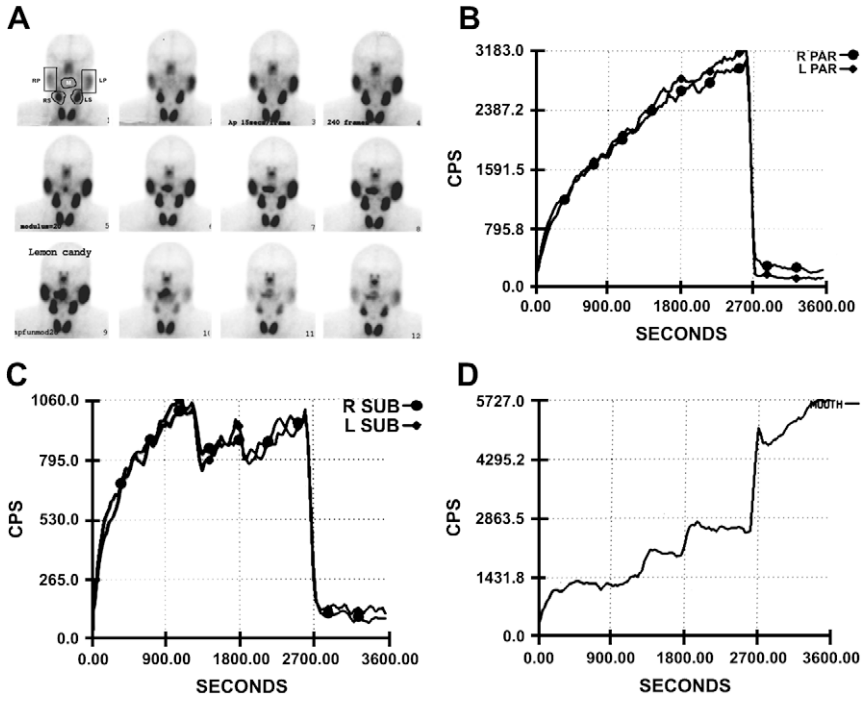

Fig. 3. 54- year-old woman complaining of moderately dry mouth. (*A*) Composite of ciné replay. Each image is the 5-minute sum of 20 frames, recorded at 15 s/frame. Regions of interest are outlined over the following: right parotid gland (RP), left parotid gland (LP), right submandibular (RS), left submandibular (LS), and mouth or oral cavity (M). A gustatory stimulus of lemon candy begins at 2700 seconds (45 minutes). (*B*) Parotid function time–activity curves (TAC). A six-point moving average smoothing kernel has been applied. Both parotids show monotonic accumulation of activity until the gustatory stimulus. Parotid gland contents then are excreted into the oral cavity with a calculated stimulated excretion fraction of 90% and 95% respectively. Uptake grade of both glands is 1 and discharge is also 1. (*C*) Submandibular TAC. Activity accumulates monotonically until circa 17 minutes, after which two episodes of spontaneous oral excretion occur, preceding gustatory stimulation. Right and left submandibular excretion fractions are both 97%. Note that maximum counts per second of submandibulars are roughly one third those of the parotid glands because of resting excretion in the former. Both uptake curve and excretion grades are 1. (*D*) Oral cavity TAC showing irregular unstimulated activity accumulation, almost entirely caused by submandibular excretion, leading to a reciprocal or mirror image relationship between oral and submandibular TACs, most striking at the initiation of protracted gustatory stimulus. Assignment of RP-LP-RS-LS uptake grades (1 + 1 + 1 + 1) and RP-LP-RS-LS discharge grades (1 + 1 + 1 + 1) and summing yields a normal functional index of 8.

Each laboratory likely will find it necessary to establish its own reference ranges. Loss of both resting and stimulated secretion represents an escalation of severity and, while seen more often in the submandibulars, may exist in the parotid glands as well, a level 4 severity (**Fig. 4**).

Were secretory alterations the only salivary infelicities encountered, interpretation would be relatively straightforward. Trapping/uptake behavior and its parenchymatous underpinning almost invariably fabricate the template upon which secretory malfunctions operate, however. For example, if uptake is undetectable, so is

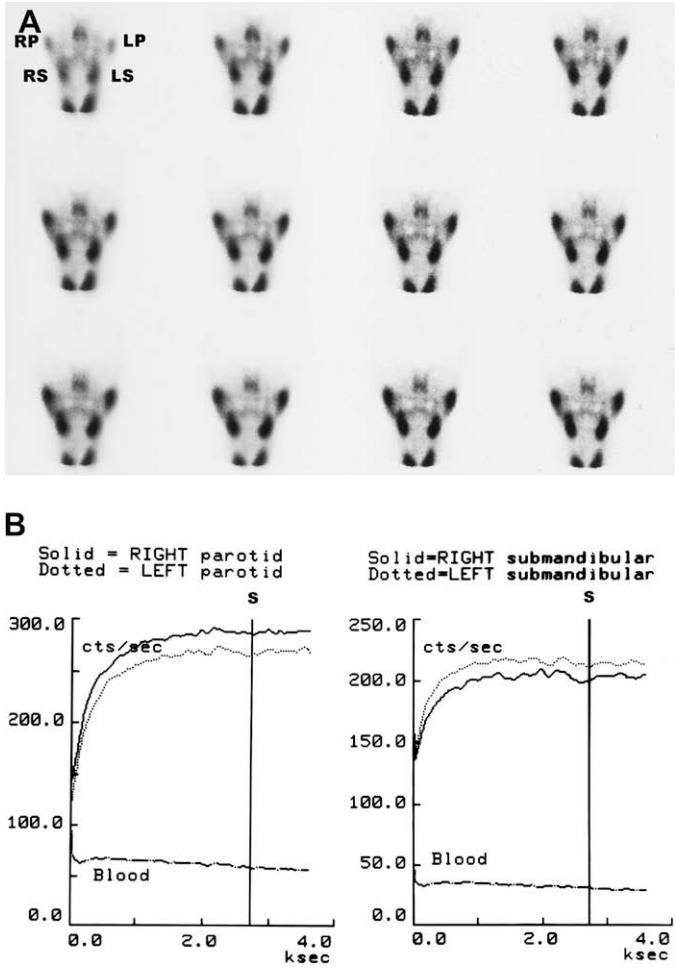

Fig. 4. 46-year-old woman with Sjögren's syndrome and unstimulated salivary flow rate of 0.05 mL/min. (*A*) Composite of ciné replay. (*B*) Time–activity curves of parotid glands and submandibulars. Uninterrupted accumulation of activity in both sets of glands, impervious to continuous gustatory stimulation (S) from 45 minutes. Uptake grade of all glands is 1. Resting discharge of parotid glands may or may not be abnormal, but there is a deficit in stimulated discharge, a grade 3 defect. Both submandibulars show neither resting nor stimulated discharge, a grade 4 defect. Global stimulated excretion fraction is essentially zero. Assignment of uptake (1 + 1 + 1 + 1) and discharge (3 + 3 + 4 + 4) grades to each of the four glands and summation yields a functional index of 18, a midrange severity. Complete preservation of global glandular uptake capability, however, suggests an intact underlying salivary parenchyma coexisting with significant but possibly treatable autonomic dysregulation.

discharge, signaling a fifth (admittedly arbitrary) class of dysfunction. Because many quantitative indices are suspect, classification of uptake behavior by means of curve perusal a la Mita might seem preferable. Roughly analogous to discharge, a four-level severity code of normal, median, flat, and sloped curves may be assigned to each gland. Quantification of tracer uptake proves difficult by this approach, however.

Although the authors have had no experience with the early uptake slope of Demangeat and colleagues, their findings are plausible and, if confirmed, might offer a semiquantitative alternative to TAC-derived classification of uptake.

Optimal interpretation requires synthesis of uptake and discharge indicators, each weighted for severity, distribution, and ubiquity. Pending further progress, the authors apprehend this to favor an interpretative system based on high temporal resolution ciné revue, oral activity monitoring, uptake slope, resting discharge activity, and the stimulated excretion fraction.

Clinical Objectives of Salivary Scintigraphy

What are the aims of the rheumatologist who encounters a patient who has a chief complaint of dry mouth? Following a careful history and physical examination, it is incumbent on the physician to obtain objective confirmation of symptomatic xerostomia, most often by documenting diminished salivary flow rates, even though there is a weak association between subjective symptoms and objective hypoptyalism.[59,60]

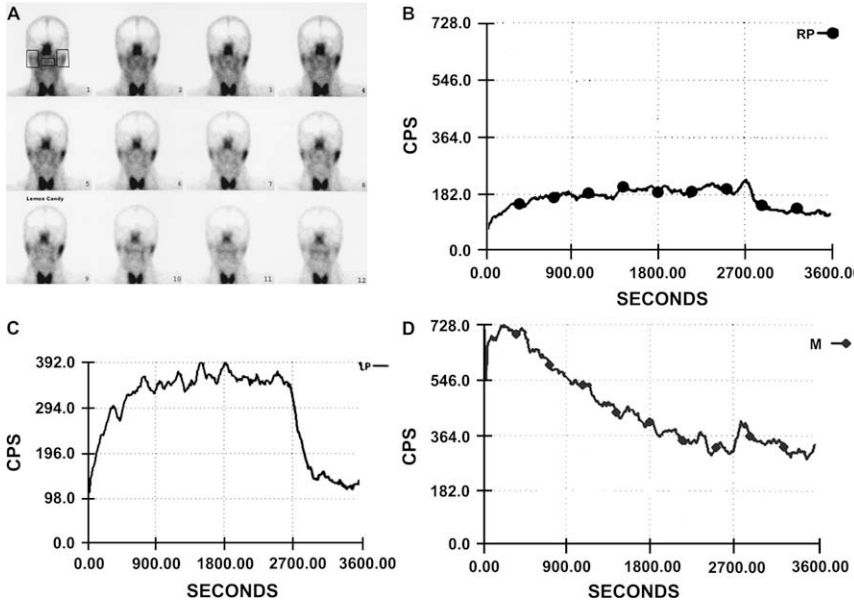

Fig. 5. 59-year-old woman with Sjögren's syndrome, severe xerostomia, and unstimulated salivary flow rate of 0.05 mL/min. (*A*) Composite of ciné replay with regions of interest drawn over the parotid glands and the oral cavity. (*B*) Right parotid time–activity curves (TAC) showing flat (grade 3) uptake curve and a stimulated excretion fraction of less than 50%, a grade 3 discharge. (*C*) Left parotid TAC with a median (grade 2) uptake and borderline stimulated excretion fraction of 66%, suggesting deficient stimulated discharge, a grade 3 failure. Minimal but observable periods of resting discharge occur. (*D*) Oral cavity TAC showing monotonic decline in activity, occasioned by a combination of minor parotid resting discharge and swallowing of saliva. Stimulated salivary discharge at 45 minutes results in a minor bump in oral count rate. Neither submandibular gland shows detectable uptake or discharge, grade 4 uptake, and grade 5 discharge severity. Summation of 3 + 2 + 4 + 4 uptake and 3 + 1 + 5 + 5 discharge yields a functional index of 27, with loss of functional parenchyma accounting for most of the patient's xerostomia. The distribution and severity of functional deficits are irregular. Sialogogic treatment with pilocarpine produced only a modest increase of salivary flow to 0.07 mL/min.

Most patients who have xerostomia first lose unstimulated salivary flow, most often that of the submandibular glands, because of disturbances of the parasympathetic autonomic pathways.[35,61]

If resting or stimulated flow rates are diminished, it is usually desirable to enquire into the nature of the physiologic derangement(s) responsible for the salivary dysfunction, because the severity, pervasiveness, distribution, and type of abnormality may prove helpful in clinical management. It is at this point during the diagnostic and therapeutic narrative that salivary scintigraphy may be of value.

Capabilities and Limitations of Salivary Scintigraphy

When the rheumatologist orders a salivary scintigraphic study, it must be with an awareness of its interpretative strengths and weaknesses. When asked the appropriate questions, scintigraphy is capable of providing clinically useful answers. Foremost of these is the question of whether the patient has objective evidence of impaired

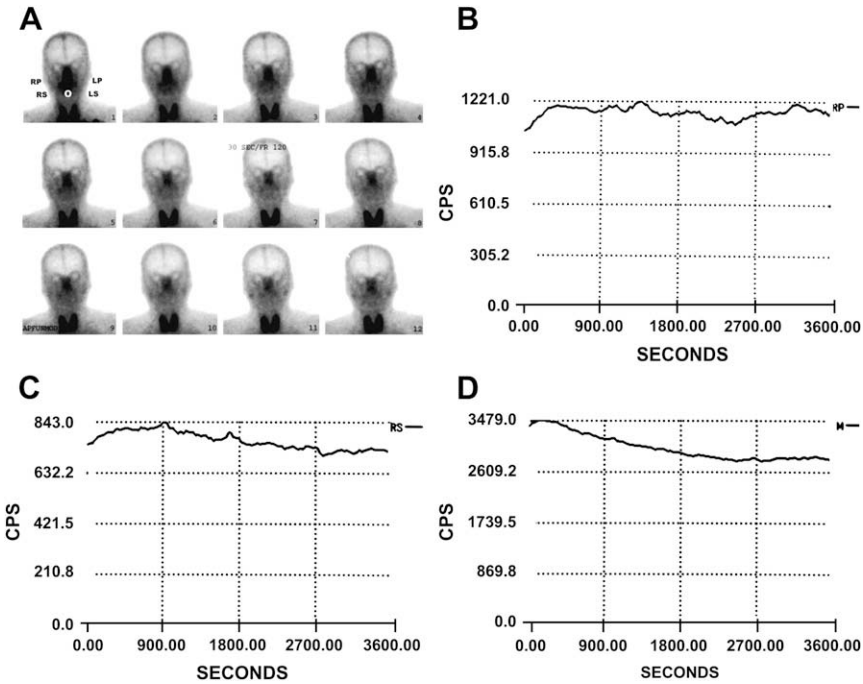

Fig. 6. 62-year-old woman with sicca syndrome for 5 years and primary biliary cirrhosis for 8 years. No history of radiation. (*A*) Composite of ciné replay with regions of interest drawn over the four salivary glands and the oral cavity. (*B*) Right parotid TAC showing sloped (grade 4) uptake curve essentially paralleling the blood background (not displayed). No trapping or uptake is detectable, and a stimulated excretion fraction cannot be calculated. (*C*) Right submandibular TAC recapitulating parotid TAC. (*D*) Oral cavity TAC revealing no incoming resting or stimulated salivary activity. Coding for composite salivary function is 4 + 4 + 4 + 4 for uptake and 5 + 5+ 5 + 5 for discharge, an upper limit functional index of 36. The study suggests that this patient with a long symptomatic history suffers from profound parenchymal destruction uniformly affecting the entire major salivary apparatus. Because of this, the integrity of glandular autonomic components cannot be evaluated. A sialogogic approach to therapy unlikely would prove effective.

salivary function, and scintigraphy answers this with a maximum sensitivity exceeding 95%.[40,62] If impaired function is demonstrable by flow rate testing or scintigraphy, the latter modality can document the size, position, and number of functioning salivary glands. It can characterize and summarize functional defects. For each gland, it can differentiate changes caused largely by irreversible parenchymal loss from neurogenically mediated excretory dysfunction that may be amenable to an increasing array of therapeutic modalities (**Figs. 5** and **6**). It may, by providing objective data, contribute to longitudinal clinical trials apropos of disease progression and therapeutic outcome prediction and monitoring. It is these capabilities that comprise scintigraphy's value, not its dubious tilt with specific etiologic windmills.

Scintigraphy cannot provide etiologic insights. That is, it cannot solve the differential diagnostic possibilities encountered in rheumatologic practice. Aside from a characteristic tendency shared with radiated patients toward high-grade dysfunction, SS sufferers show defects indistinguishable from those with chronic sialadenitis, drug effects, and metabolic derangement.[52,63,64]

The Future of Salivary Scintigraphy

From the perspective of organized nuclear medicine, salivary scintigraphy is a niche procedure seldom performed in routine practice. But for those rheumatologists interested in SS and actively overseeing dry mouth clinics, it assumes rather more import. Nevertheless, this diagnostic procedure probably is destined to retain its secondary status in the American–European Consensus Group's SS classification scheme. The clinical utility of scintigraphy in SS and related disorders, however, could be enhanced.

Improvement only will accompany a standardization of test protocol and interpretation by consensus among practicing rheumatologists and their nuclear medicine colleagues. In 1999, the Society of Nuclear Medicine began publishing a series of guidelines outlining standardized elements of procedures designed to obtain a high-quality examination among many organ systems, including gastroenterology. This activity continues apace but has not engaged functional salivary imaging. The American College of Radiologists' salivary gland imaging protocol lacks detail. Until and unless convocation of the willing materializes, salivary scintigraphy will continue to play a valuable but limited role in the diagnosis and management of SS, its efficacy hampered by its diversity of process and interpretation. In the meantime, the American–European Consensus Group might consider updating "delayed uptake, reduced concentration, and/or delayed excretion of tracer" to a less specific descriptive evocation of uptake and excretion, resting and stimulated.

REFERENCES

1. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61(6):554–8.
2. Bowman SJ, Pillemer S, Jonsson R, et al. Revisiting Sjögren's syndrome in the new millennium: perspectives on assessment and outcome measures. Report of a workshop held on 23 March 2000 at Oxford, UK. Rheumatology 2001; 40(10):1180–8.
3. Pillemer SR, Smith J, Fox PC, et al. Outcome measures for Sjögren's syndrome, April 10-11, 2003, Bethesda, Maryland, USA. J Rheumatol 2004;31(1):143–9.
4. Mandl T, Jacobsson L, Lilja B, et al. Disturbances of autonomic nervous function in primary Sjögren's syndrome. Scand J Rheumatol 1997;26(5):410–6.

5. Wright RA, Grant IA, Low PA. Autonomic neuropathy associated with sicca complex. J Auton Nerv Syst 1999;75(1):70–6.
6. Vivino FB, Al-Hashimi I, Khan Z, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren's syndrome. Arch Intern Med 1999;159(2):174–81.
7. Cooper RA, Cowan RA, Owens SE, et al. Does salivary gland scintigraphy predict response to pilocarpine in patients with postradiotherapy xerostomia? Eur J Nucl Med 1999;26(3):220–5.
8. Rosas J, Ramos-Casals M, Ena J, et al. Usefulness of basal and pilocarpine-stimulated salivary flow in primary Sjögren's syndrome. Correlation with clinical, immunological, and histological features. Rheumatology (Oxford) 2002;41(6):670–5.
9. Li J, Ha YM, Ku NY, et al. Inhibitory effects of autoantibodies on the muscarinic receptors in Sjögren's syndrome. Lab Invest 2004;84(11):1430–8.
10. Nakayamada S, Saito K, Umehara H, et al. Efficacy and safety of mizoribine for the treatment of Sjögren's syndrome: a multicenter open-label clinical trial. Mod Rheumatol 2007;17(6):464–9.
11. Jadvar H, Bonyadlou S, Iagaru A, et al. FDG PET-CT demonstration of Sjögren's sialoadenitis. Clin Nucl Med 2005;30(10):698–9.
12. Basu S, Houseni M, Alavi A. Significance of incidental flourodeoxyglucose uptake in the parotid glands and its impact on patient management. Nucl Med Commun 2008;29(4):367–73.
13. McAfee JG, Fueger CF, Stern HS, et al. Tc-99m pertechnetate for brain scanning. J Nucl Med 1964;5(11):811–27.
14. Ahiner BH, Lind MG. The capacity of irradiated rabbit submandibular glands to concentrate 99mTcO4 pertechnetate. Eur Arch Otorhinolaryngol 1993;249(8):462–5.
15. Taplin GV, Dore EK, Johnson DE. Suspensions of radioalbumin aggregate for photoscanning the liver, spleen, lungs, and other organs. UCLA-519. UCLA Rep 1963;86(11):1–39.
16. Harper PV, Beck R, Charleston D, et al. Optimization of a scanning method using 99mTc. Nucleonics 1964;22(1):50–4.
17. Bömer W, Grünberg H, Moll E. Die szintigraphische Darstellung der Kopfspeicheldrusen mit Technetium-99m. Med Welt 1965;42(43):2378–90.
18. Schall GL, Anderson LG, Wolf RO, et al. Xerostomia in Sjögren's syndrome. JAMA 1971;216(13):2109–16.
19. Schall GL, Larson SM, Anderson LG, et al. Quantification of parotid gland uptake of pertechnetate using a gamma scintillation camera and a region-of-interest system. Am J Roentgenol Radium Ther Nucl Med 1972;115(4):689–97.
20. Stephen KW, Robertson JW, Harden RM. Quantitative aspects of pertechnetate concentration in human parotid and submandibular glands. Br J Radiol 1976; 49(588):1028–32.
21. Häusler RJ, Ritschard J, N'Guyen VT, et al. Differential diagnosis of xerstomia by quantitative salivary gland scintigraphy. Ann Otol Rhinol Laryngol 1977; 86(3 Pt 1):333–41.
22. Arrago JP, Rain JD, Brocheriou C, et al. Scintigraphy of the salivary glands in Sjögren's syndrome. J Clin Pathol 1987;40(12):1463–7.
23. Wang S, Zou Z, Zhu J. Sequential quantitative scintigraphy of parotid glands with chronic inflammatory diseases. J Oral Maxillofac Surg 1992;50(5):456–65.
24. Bohuslavizki KH, Brenner W, Wolf H, et al. Value of quantitative salivary gland scintigraphy in the early stage of Sjögren's syndrome. Nucl Med Commun 1995;16(11):917–22.

25. Umehara I, Yamada I, Murata Y, et al. Quantitative evaluation of salivary gland scintigraphy in Sjögren's syndrome. J Nucl Med 1999;40(1):64–9.
26. Daniels TE, Powell MR, Sylvester RA, et al. An evaluation of salivary scintigraphy in Sjögren's syndrome. Arthritis Rheum 1979;22(8):809–14.
27. Delpassand ES, Zare F, Broussard W, et al. Functional ratios of normal salivary glands using dual detector gamma camera and geometric means. Clin Nucl Med 1997;22(3):200 [abstract].
28. van Acker F, Flamen P, Lambin P, et al. The utility of SPECT in determining the relationship between radiation dose and salivary gland dysfunction after radiotherapy. Nucl Med Commun 2001;22(2):225–31.
29. Hermann GA, Vivino FB, Shnier D, et al. Variability of quantitative salivary indices in normal subjects. J Nucl Med 1998;39(7):1260–3.
30. Harden RM, Hilditch TE, Kennedy I, et al. Uptake and scanning of the salivary glands in man using pertechnetate-^{99m}Tc. Clin Sci 1967;32(1):49–55.
31. Malpani BL, Samuel AM, Ray S. Differential kinetics of parotid and submandibular gland function as demonstrated by scintigraphic means and its possible implications. Nucl Med Commun 1995;16(8):706–9.
32. Aung W, Murata Y, Ishida R, et al. Study of quantitative oral radioactivity in salivary gland scintigraphy and determination of the clinical stage of Sjögren's syndrome. J Nucl Med 2001;42(1):38–43.
33. Han R, Zagar I, Mitrovic S, et al. Salivary excretory index—quantification of the ascorbic acid response in dynamic radionuclide sialography. Med Pregl 1993; 46(Suppl 1):54–5.
34. Parret J, Peyrin JO. Radioisotopic investigations in salivary pathology. Clin Nucl Med 1979;4(6):250–61.
35. Kohn WG, Ship JA, Atkinson JC, et al. Salivary gland ^{99m}Tc-scintigraphy: a grading scale and correlation with major salivary gland flow rates. J Oral Pathol Med 1992;21(2):70–4.
36. Sugihara T, Yoshimura Y. Scintigraphic evaluation of the salivary glands in patients with Sjögren's syndrome. Int J Oral Maxillofac Surg 1988;17(2):71–5.
37. De Rossi G, Focacci C. A computer-assisted method for semiquantitative assessment of salivary gland diseases. Eur J Nucl Med 1980;5(6):499–503.
38. Valdés-Olmos RA, Keus RB, Takes RP, et al. Scintigraphic assessment of salivary function and excretion response in radiation-induced injury of the major salivary glands. Cancer 1994;73(12):2886–93.
39. Demangeat R, Didon-Poncelet A, Cherfan J, et al. Stimulated salivary pertechnetate clearance revisited: correlation with dynamic scintigraphic indices in sicca syndrome. Clin Nucl Med 2000;25(11):888–94.
40. Chisin R, Markitziu A, Hoffer S, et al. The clinical value of quantitative dynamic scintigraphy in salivary gland disorders. Int J Rad Appl Instrum B 1988;15(3): 313–7.
41. De Jager JP, Choy D, Fleming A. Salivary scanning in rheumatoid arthritis with sicca syndrome. Ann Rheum Dis 1984;43(4):610–2.
42. Hakansson U, Jacobsson L, Manthorpe R, et al. Salivary gland scintigraphy in subjects with and without symptoms of dry mouth and/or eyes, and in patients with primary Sjögren's syndrome. Scand J Rheumatol 1994;23(6):326–33.
43. Kosuda S, Suzuki K, Kawakami R, et al. Reassessment of usefulness of salivary scintigraphy in diagnosis of Sjögren's syndrome. Kaku Igaku 1993;30(2):161–70.
44. Mita S, Kohno M, Matsuoka Y, et al. Diagnostic availability of RI-sialography in Sjögren's syndrome. Ryumachi 1981;21(4):305–16.

45. Markusse HM, Pillay M, Breedveld FC. The diagnostic value of salivary gland scintigraphy in patients suspected of primary Sjögren's syndrome. Br J Rheumatol 1993;32(3):231–5.
46. Henriksen AM, Nossent HC. Quantitative salivary gland scintigraphy can distinguish patients with primary Sjögren's syndrome during the evaluation of sicca symptoms. Clin Rheumatol 2007;26(11):1837–41.
47. Roescher N, Illei GG. Can quantified salivary gland scintigraphy results aid diagnosis of patients with sicca symptoms? Nat Clin Pract Rheumatol 2008;4(4):178–9.
48. Scott J, Cawood JI, Grime JS, et al. Histological evaluation of quantitative scintigraphy of the salivary glands in a primate model. Int J Oral Surg 1984;13(1):45–52.
49. Mauch E, Volk C, Kratzsch G, et al. Neurological and neuropsychiatric dysfunction in primary Sjögren's syndrome. Acta Neurol Scand 1994;89(1):31–5.
50. Mori K, Iijima M, Koiki H, et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. Brain 2005;128(11):2518–34.
51. Hermann GA, Vivino FB, Goin JE. Scintigraphic features of chronic sialadenitis and Sjögren's syndrome: a comparison. Nucl Med Commun 1999;20(12): 1123–32.
52. Nishiyama S, Miyawaki S, Yoshinaga Y. A study to standardize quantitative evaluation of parotid gland scintigraphy in patients with Sjögren's syndrome. J Rheumatol 2006;33(12):2470–4.
53. Coll J, Porta M, Rubiés-Prat J, et al. Sjögren's syndrome: a stepwise approach to the use of diagnostic tests. Ann Rheum Dis 1992;51(5):607–10.
54. Martinez-Lázaro R, Cortés-Blanco A, Velilla J. A pilot study of the salivary scintigraphy diagnostic performance in a Spanish population with with Sjögren's syndrome diagnosed by the European criteria. Ann Rheum Dis 2001;60(3):302–3.
55. Fossaluzza V, De Vita S, Geatti O. Sequential salivary scintigraphy in Sjögren's syndrome: proposal for a new method of evaluation. Clin Exp Rheumatol 1990; 8(5):469–74.
56. Blue PW, Jackson JH. Stimulated salivary clearance of technetium-99m pertechnetate. J Nucl Med 1985;26(3):308–11.
57. Malpani BL, Jaiswar RK, Samuel AM. Variability of quantitative scintigraphic salivary indices in healthy subjects. J Nucl Med 1999;40(12):2129–30.
58. Malpani BL, Jaiswar RK, Samuel AM. Noninvasive scintigraphic method to quantify unstimulated secretions from individual salivary glands. Auris Nasus Larynx 1999;26(4):453–6.
59. Fox PC, Busch KA, Baum BJ. Subjective reports of xerostomia and objective measures of salivary gland performance. J Am Dent Assoc 1987;115(4):581–4.
60. Hay EM, Thomas E, Pal B, et al. Weak association between subjective symptoms of and objective testing for dry eyes and dry mouth: results from a population-based study. Ann Rheum Dis 1998;57(1):20–4.
61. Pijpe J, Kalk WW, Bootsma H, et al. Progression of salivary gland dysfunction in patients with Sjögren's syndrome. Ann Rheum Dis 2007;66(1):107–12.
62. Dugonjić S, Ajdinović B, Stefanović D, et al. Diagnostic validity of dynamic salivary gland scintigraphy with ascorbic acid stimulation in patients with Sjögren's syndrome: comparison with unstimulated whole sialometry. Vojnosanit Pregl 2008;65(1):41–6.
63. Booker J, Howarth D, Taylor L, et al. Appropriate utilization of semiquantitative analysis in salivary scintigraphy. Nucl Med Commun 2004;25(12):1203–10.
64. Adams BK, Al Attia HM, Parkar S. Salivary gland scintigraphy in Sjögren's syndrome: are quantitative indices the answer? Nucl Med Commun 2003;24(9): 1011–6.

Treatment of Dry Eye Disease by the Non-Ophthalmologist

Gary N. Foulks, MD, FACS

KEYWORDS

• Dry eye • Sjögren's syndrome • Cyclosporine • Secretagogues

Physicians caring for patients with Sjögren's syndrome often face a particularly difficult task in managing the dry eye that occurs with this disease. The discomfort produced by the condition and the fluctuation of vision attendant to tear film instability are often the most annoying of the clinical symptoms. The understanding of dry eye disease in both its clinical expression and underlying etiopathology has expanded over the past 10 years with implications for management and therapy. The array of potential treatments both topical and systemic has evolved to provide a much more targeted and effective arsenal from which the clinician may choose.

PRESENT UNDERSTANDING OF DRY EYE DISEASE AND IMPLICATIONS FOR THERAPY

A recent international workshop designed to collate and critique in an evidence-based manner the accumulated knowledge concerning dry eye disease and its treatment published a comprehensive report in 2007.[1] The Dry Eye Workshop provided guidance to clinicians and researchers regarding the definition, classification, epidemiology, and research findings, and treatment guidelines for dry eye disease.

The consensus definition of dry eye disease was stated to be that dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[2] This definition expands the scope of the disease to include effects on visual acuity and discomfort and damage to the ocular surface through both inflammation of the tissues and hyperosmolarity of the tear film.[3]

The classification of dry eye disease proposed three distinct schemas: (1) an etiopathologic, (2) a mechanistic, and (3) a severity-based description.[2] **Fig. 1** depicts the etiopathologic classification and identifies both an aqueous-production deficit and an evaporative category of dry eye disease. Although clinical expression of either

Supported by an unrestricted grant from Research to Prevent Blindness, New York, NY.
Department of Ophthalmology and Visual Sciences, University of Louisville School of Medicine, 301 East Muhammad Ali Boulevard, Louisville, KY 40202, USA
E-mail address: gnfoul01@louisville.edu

Rheum Dis Clin N Am 34 (2008) 987–1000
doi:10.1016/j.rdc.2008.08.008 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

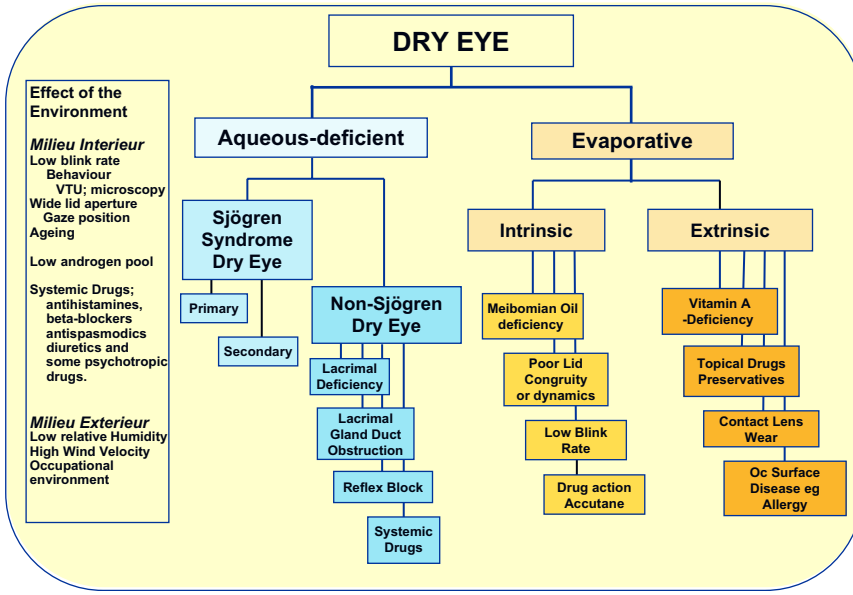

Fig. 1. Etiopathologic classification of dry eye disease. (*From* Ethis Communications. Report of the International Dry Eye Workshop. Ocul Surf 2007;5:77; with permission.)

one or the other type of dry eye is possible, the most common occurrence is a combination of the two types, suggesting that treatment options need to address both mechanisms of disease. The mechanistic schema describing dry eye disease is portrayed in **Fig. 2**, which details the extensive interactivity and cyclical effects of hyperosmolarity of the tear film, instability of the tear film, and inflammatory activity of the ocular surface system. The severity-based classification is described in **Table 1** and illustrates that sequential changes in the degree of discomfort, instability of the tear film, increasing signs of inflammation, and evolving damage to the ocular surface indicate progressive disease. Based on this analysis of the nature and clinical manifestation of dry eye, recommendations for therapy have been made.[4] The implications of this assessment of dry eye are significant for all patients with dry eye but particularly patients with Sjögren's syndrome, because the severity of dry eye disease and the role of inflammation in the pathogenesis of the Sjögren's syndrome–related dry eye is particularly prominent in those patients.[5]

Review of the epidemiology of dry eye disease also reveals information about the underlying predispositions to the disease and its association with age, gender, and general health. Dry eye disease is more common in women than men; increases with advancing age; and often is associated with changes in hormone levels, particularly androgenic hormones.[6–11] The association of dry eye with systemic disease of immune-mediated pathogenesis has also been well documented, Sjögren's syndrome being the prime example.[12] Although the prevalence of dry eye varies widely across international populations from a reported high of 38% in some Asian studies to more consistent reports of 12% to 15% in North American populations above age 55, the projected number of affected patients is considerable.[13–16] Increasing awareness of the prevalence of dry eye disease and the quality-of-life changes it produces alerts to the fact that the frequency of the condition is increasing as the population

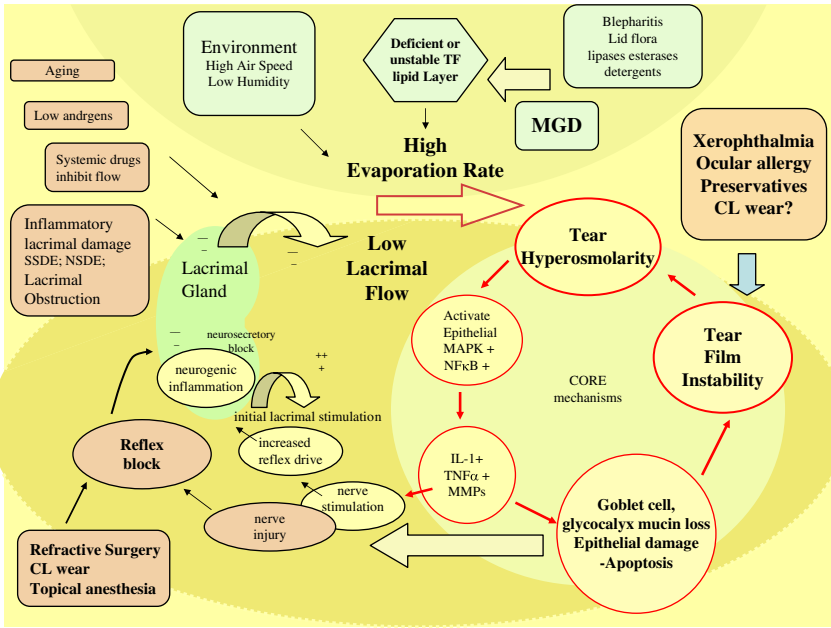

Fig. 2. Mechanistic classification of dry eye disease. (*From* Ethis Communications. Report of the International Dry Eye Workshop. Ocul Surf 2007;5:85; with permission.)

ages and as women outlive men. It is now recognized as an ever more important public health issue.[17]

The present understanding of the pathogenesis of dry eye disease also has implications for management and therapy. Although once considered only a lack of tears on the ocular surface, the disease is now recognized as a complex and multifactorial process with interaction of not only low volume of tear fluid, but also instability of the tear film with subsequent hypertonicity of the preocular fluid that is able not only directly to damage surface epithelial cells but also to provoke and stimulate inflammatory reaction in the ocular tissues.[18–20] Accumulation of inflammatory T lymphocytes in the lacrimal and subconjunctival tissue is associated with release of proinflammatory cytokines and matrix-metalloproteinases in both tears and tissues.[21–25] The observation that such inflammatory processes can be mitigated by topical anti-inflammatory treatments, such as corticosteroids and immunomodulating agents, opens the door to additional therapeutic strategies.[26–30]

PECULIARITIES OF DRY EYE DISEASE IN SJÖGREN'S SYNDROME

It is ironic that the first description of keratoconjunctivitis sicca in Sjögren's syndrome was that of an inflammatory disease, yet the subsequent emphasis became the lack of tear fluid on the eye.[31] The recognition that keratoconjunctivitis sicca (dry eye) occurred commonly in patients with rheumatoid arthritis and Sjögren's syndrome and that the severity of the disease was greater than non–Sjögren's-associated dry eye has led to other aspects of inflammation occurring with dry eye.[32,33] The increased prevalence of meibomian gland disease and the evaporative form of dry eye has been documented in Sjögren's syndrome patients.[34] These findings carry therapeutic implications.

Table 1
Severity classification of dry eye disease

Dry Eye Severity Level	1	2	3	4
Discomfort severity and frequency	Mild or episodic occurs under environ stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying or activity limiting episodic	Annoying, chronic, or constant limiting activity	Constant or possibly disabling requires signs and symptoms
Conjunctival injection	None to mild	None to mild	+/−	+/++
Conjunctival staining	None or mild	Variable	Moderate to marked	Marked
Corneal staining (severity, location)	None or mild	Variable	Marked central	Severe punctate erisions
Corneal, tear signs	None to mild	Mild debris ↓ meniscus	Filamentary keratitis, mucus clumping ↑ tear debris	Filamentary keratitis Epithelial defect ulceration
Lid, meibomian glands	Variable	Variable	Frequent	Trichiasis Keratinization Symblepharon
Tear break up time (seconds)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5 min)	Variable	≤10	≤5	≤2

From Ethis Communications. Report of the International Dry Eye Workshop. Ocul Surf 2007;5:88; with permission.

MANAGEMENT OF DRY EYE DISEASE

An effective strategy for the management of dry eye disease includes attention to the patient's lifestyle and specific pharmacologic intervention. The aggravating factors to dry eye and predisposition to symptoms of irritation are well known. Smoking has been identified as a risk factor.[35] Such activities as prolonged reading, prolonged staring at a video display terminal, airplane flight, and the use of antihistamines or anticholinergic medications all increase symptoms by worsening tear film stability and volume.[36,37] Often simple modification of these behaviors or the use of room humidifiers to increase ambient humidity helps to reduce symptoms, but rarely do such adjustments completely control symptoms. Ensuring that there is no intercurrent blepharitis or inflammation of the anterior eyelid margin is essential. Nevertheless, topical or systemic medications are necessary adequately to treat the disease. The guidelines proposed by the Delphi Panel and the Dry Eye Workshop based on severity of disease are worthwhile to help guide therapy (**Fig. 3**, **Table 2**).[4,37]

SPECIFIC THERAPY OF DRY EYE DISEASE

Lubricant Therapy

The mainstay treatment of dry eye disease has been lubrication with a variety of artificial tear supplements.[38] Many of these have been fortified with polymers, emollients, vitamins, and other additives.[39] Nonetheless, such treatment is palliative and not corrective of the underlying pathology of the disease. Recognition of the fact that elevated osmolarity of the tear film is both damaging to the surface epithelium and stimulatory to inflammation necessitates attempts to reduce the osmolarity of the tear film with instilled drops that are hypotonic to the normal tear but otherwise of

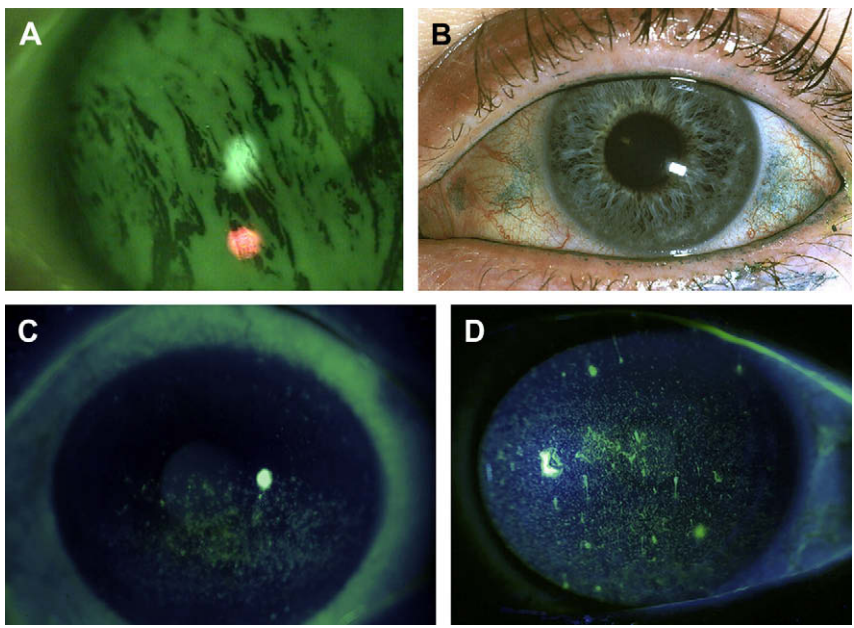

Fig. 3. Common objective signs of dry eye disease used to grade severity. (*A*) Tear break-up time (fluorescein). (*B*) Conjunctival staining with lissamine green. (*C*) Corneal staining with fluorescein. (*D*) Filaments on the cornea in areas of confluent fluorescein staining.

Table 2
Treatment recommendations by severity level

Level 1	Education and environmental and dietary modifications Elimination of offending systemic medications Artificial tear substitutes, gels and ointments Eye lid therapy
Level 2	*If level 1 treatments are inadequate, add* Anti-inflammatory drugs Tetracyclines (for meibomianitis, rosacea) Punctal plugs Secretogogues Moisture chamber spectacles
Level 3	*If level 2 treatments are inadequate, add* Serum Contact lenses Permanent punctal occlusion
Level 4	*If level 3 treatments are inadequate, add* Systemic anti-inflammatory agents Surgery (lid surgery, tarsorrhaphy; mucus membrane, salivary gland, amniotic membrane transplantation)

Modified from Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea 2006;25:900–7; with permission.

a composition to match physiologic tear (TheraTears, Advanced Therapy, Woburn, Massachusetts).[18,20,40,41] This replacement tear can improve the health of the ocular surface, but unfortunately the duration of effective reduction of tear film osmolarity is short-lived following topical instillation.[42]

Several enhanced tear formulations have been developed in the last 5 years with the goal of increasing retention of the topical agent and protecting the ocular surface while stabilizing the tear film. A novel gel-forming formulation of HP-Guar base has been shown to reduce friction on the ocular surface while prolonging tear break-up time. Systane (Alcon Laboratories, Fort Worth, Texas) works well alone to increase lubricity of the tear film, but has also been demonstrated to enhance the effect of topical cyclosporine treatment of dry eye.[43]

The use of lipids to create topical emulsions that stabilize the tear film was occasioned by development of a vehicle for delivery of cyclosporine. The formulation tested very well in clinical trials as a vehicle control in the Phase II and III clinical trials of topical cyclosporine treatment of dry eye disease, and it has subsequently been marketed as a tear stabilizer.[29] It is available in an over-the-counter product (Refresh Endura, Allergan, Irvine, California) and is composed of a lipid emulsion of castor oil that also includes glycerin, polysorbate 80, and sodium hydroxide (to adjust the pH). Retardation of evaporation of the tear film is the most likely explanation of effectiveness and it has been shown to stabilize the tear film and improve tear break up time.[44]

A more recent approach is the development of a metastable lipid emulsion, Soothe (Bausch and Lomb, Rochester, New York), which mimics the polar and nonpolar lipid components of the superficial lipid layer of the tear film by rapidly separating into its multiple oil and water phases.[45] In a double-masked, subject-paired study, Korb and associates[45] demonstrated an increase in lipid layer thickness in subjects reporting dry eye symptoms along with improvement of symptoms. The eye drop containing Restoryl, the active ingredient of Soothe, more than doubled lipid layer thickness.

Tear supplementation and modulation of the effects of a disturbed tear film by targeted therapy with enhanced lubricants to protect the ocular surface continue to be an important part of management of the dry eye, especially patients with mild or episodic disease that is aggravated by environmental conditions or physical activities, such as working with computers and videogames, but also in the patient with chronic dry eye disease. An important consideration with any topically applied drop concerns the frequency of exposure of the ocular surface to preservatives in the applied solution. If application is more frequent than three or four times per day, the use of unpreserved solutions is advisable to prevent the irritation and damage of the surface that occurs with preservatives, particularly surface active agents, such as benzalkonium chloride.

Osmoprotective Therapy

Other methods of mitigating the deleterious effect of increased tear film osmolarity on the ocular surface use the concept of osmoprotection of surface cells with use of compatible osmolyte molecules. Based on the biologic concepts of controlling osmotic stress to epithelial cells by incorporating compatible osmolytes, molecules that are internalized to the cell serve to counterbalance external osmotic stress. The compatible solutes abrogate some of the damage induced by the hypertonic tear.[46,47] Such solutes include glycerin and taurine that are compatible with intracellular structures. Because osmoprotectants are internalized by cells, residence time on the surface of the eye and the duration of benefit is increased beyond the physical residence time of typical artificial tears. The product, Optive (Allergan, Irvine, California), which reached the market in early 2007, is a practical and improved artificial tear that holds promise for incremental benefit in treating patients with signs or symptoms caused by hyperosmotic compromise of the ocular surface.

Anti-Inflammatory Therapy

Topical steroids

With the increased appreciation of the role of inflammation in the pathogenesis of dry eye disease, new emphasis has been placed on anti-inflammatory therapy. This approach is particularly valuable in the case of dry eye associated with Sjögren's syndrome because of the systemic inflammation and the greater degree of ocular surface inflammation. Such therapy provokes some anxiety in the nonophthalmologist practitioner who has been previously advised to minimize the use of topical steroids because of possible side effects of ocular hypertension (glaucoma) or cataracts. Nonetheless, judicious use of topical steroids has a place in treatment of dry eye when used in pulse fashion in highly symptomatic patients or as adjunctive treatment to minimize stinging on initiation of the use of topical cyclosporine.[26,27] Use of those formulations (soft steroids) that have a lower incidence of aggravating intraocular pressure and cataracts is reasonable.[27] Lotoprednol etabonate (Lotemax, Bausch and Lomb, Rochester, New York) applied topically three or four times per day is one such option.

Topical cyclosporine

Recently, topical cyclosporine 0.05% emulsion (Restasis, Allergan, Irvine, California) has been approved for clinical use to treat those patients with decreased tear production thought to be caused by inflammation. Such treatment has been demonstrated to reduce expression of cell surface markers of both inflammation and apoptosis in conjunctival biopsies of treated dry eye patients.[45] In clinical trials reduction in the numbers of lymphocytes in conjunctival biopsies was associated with statistically

significant reductions of CD40 ($P = .049$) and CD40 ligand ($P \leq .008$) and the percentage of cells expressing Fas ($P \leq .046$).[22,30]

Clinical trials have demonstrated beneficial response to twice daily topical therapy with cyclosporine and the safety of the drug has been noted in long-term trials.[28,29,48] Topical administration of cyclosporine ophthalmic emulsion in humans results in plasma levels of cyclosporine that are undetectable in those patients receiving 0.05% cyclosporine, and very low levels in those receiving 0.1%.[29,34,49] This concentration is several orders of magnitude below trough plasma concentrations achieved during systemic therapy for psoriasis, rheumatoid arthritis, and organ transplant patients (75–400 ng/mL).[50] The adverse effects include stinging on instillation, but no evidence of superinfection or toxicity on long-term therapy.

Clinical benefit with topically applied cyclosporine 0.05% emulsion occurs in approximately 75% of patients based on the experience of a number of clinicians who have actively prescribed the drug for twice-daily dosing. Improvements in symptoms, corneal fluorescein, and rose bengal staining were observed in clinical trials, but no clear dose response relationship was demonstrated.[28] In Phase III clinical trials cyclosporine 0.05% emulsion therapy produced significantly greater improvement in blurred vision than vehicle-treated patients after 6 months ($P \leq .014$) and patients were able to reduce the frequency of supplemental artificial tear use compared with those in the vehicle group ($P \leq .006$). Increased tear production, as assessed by anesthetized Schirmer testing, was significantly greater in the cyclosporine 0.05% group than in the vehicle group ($P \leq .009$). Burning and stinging and itching decreased from baseline in the cyclosporine 0.05% group ($P \leq .024$ and $P \leq .002$, respectively) and this was consistent with improvement in clinical signs, but the symptomatic improvement was not significantly different from that occurring with the vehicle. Subsequent subset analysis of the beneficial effect of cyclosporine on tear production in those patients who were not concomitantly treated with other anti-inflammatory therapy or previously treated with punctal plugs revealed that improvement in tear production was observed in 59% of patients with 15% of patients demonstrating 10 mm or more increase in Schirmer testing.[29] Subsequent clinical trials have shown similar improvement in symptoms and ocular surface staining but without significant increase in tear secretion as measured by the Schirmer test.[51]

In addition to improved clinical outcome, immunohistologic improvement of the ocular surface abnormalities present before treatment, including reduction of cell surface markers of activated T lymphocytes and apoptotic cells in conjunctival biopsies, were noted after topical cyclosporine therapy.[52] Cyclosporine treatment reduced expression of proinflammatory cytokines and expression of HLA-DR markers.

The improvement in health of the ocular surface epithelium following cyclosporine topical therapy has also been demonstrated by restoration of the goblet cell density in conjunctival epithelium.[53] The goblet cells of the conjunctiva are a sensitive marker of damage from ocular surface disease and are decreased in chronic dry eye.[54] Because these cells provide the important gel-forming MUC5AC, which helps maintain the health of the ocular surface epithelium by protecting the surface cells, loss of goblet cells disturbs the homeostasis of the ocular surface.[55] Conjunctival goblet cell density increased following cyclosporine therapy by 191% ($P = .014$), which was significantly greater than in biopsies of vehicle-treated patients ($P = .013$).[29,53]

Essential fatty acids (omega 3)

Dietary supplementation with omega-3 essential fatty acids has been advocated as an oral therapy to reduce inflammation.[56,57] The epidemiologic observation that there was a decreased prevalence of dry eye in patients who had dietary intake of fish

containing such nutrients and the fact that these fatty acids are required in dietary supplementation because the body does not produce them has prompted the recommendation. Dietary supplementation is easily achieved with sources rich in omega 3 fatty acids, such as fish oil or flax seed oil. The findings of two small clinical trials demonstrated improvement in dry eye symptoms and signs with both oral and topical omega 3 essential fatty acids.[58,59] Multiple over-the-counter formulations for omega 3 fatty acids are available and one formulation (TheraTears Nutrition, Advanced Research, Woburn, Massachusetts) is marketed specifically for dry eye therapy.

Stimulation of Tear Secretion: Secretagogue Therapy

Stimulation of tear secretion has long been a goal in the treatment of dry eye disease but the only available agents are orally administered secretagogues that are approved for treatment of dry mouth. Indeed, the oral agents improve dry mouth symptoms better than dry eye and the tolerance of this form of therapy is limited because of cholinergic side effects of sweating and diarrhea. The available drugs are appropriate for patients with Sjögren's syndrome because dry mouth is often present and is as symptomatic as is the dry eye.[60,61] Pilocarpine (Salagen, MGI-Pharma, Bloomington, Minnesota) was the first secretagogue clinically available for use in treating xerostomia and a prospective, randomized clinical trial verified efficacy in improving symptoms of dry mouth with a smaller effect on symptoms of dry eye.[62] Cevimeline (Evoxac, Daiichi Pharmaceutical Company, Parsippany, New Jersey), also approved in the United States for treatment of symptoms of dry mouth, may be better tolerated than pilocarpine and seems effective in both xerostomia and keratoconjunctivitis sicca at the 30-mg dose.[63]

Autologous Serum Topical Therapy

When other standard therapy has failed, the topical application of autologous serum is another approach to suppressing inflammation and improving health of the ocular surface in patients with severe dry eye.[64,65] Serum contains proteins, peptides, and nutrients and growth factors that are thought to protect and heal the ocular surface. This approach to therapy has been best characterized by Tsubota and Higuchi,[66] who have described a straightforward method of preparation of the autologous serum drops with reported beneficial results of therapy. The method is cumbersome and associated with some risk of infection if contamination of the serum drops occurs. The specific molecules responsible for the healing effect of serum have not yet been definitely identified but such identification may allow more specifically targeted future therapy.[67]

FUTURE OPTIONS FOR CONSIDERATION IN THERAPY

Topical Secretagogues

Given the limitations to the use of systemic secretagogues, topical secretagogues are being developed and evaluated in clinical trials. Although not yet approved by the Food and Drug Administration, three topical secretagogues are in Phase III trials. Diquafosol (Inspire Pharmaceuticals, Durham, North Carolina) has been shown in Phase II and III clinical trials to increase aqueous tear volume and stimulate mucin secretion suggesting that this novel P2Y2 receptor agonist is safe and effective in treating dry eye. It has been shown to increase the flow of sodium and water across conjunctival membranes and to stimulate mucin production from goblet cells.[68] Improvement in symptoms and ocular surface staining in dry eye patients with clearing of the central corneal staining has been documented in clinical trials.[69] Another

Table 3
Algorithm for progressive therapy of dry eye based on severity

	Severity			
	Episodic	**Mild**	**Moderate**	**Severe**
Symptoms				
Ocular discomfort	Awareness	Frequent	Constant	Disabling
Vision changes	With activity[a]	Rare	Relieved with blink	Not relieved by blink
Dry mouth		Aware	Frequent fluids	Trouble eating
Signs				
Tear break up time	Normal >10 s	10–5 s	<5 s	Immediate
Conjunctival staining	None	Rare punctate	Diffuse punctate	Confluent
Corneal staining	None	Rare punctate	Diffuse punctate	Confluent
Filaments and erosions of cornea	None	None	None	One or more
Therapy				
Lubrication	With activity[a]	tid	qid	>6/d unpreserved
Osmoprotection		tid	qid	qid
Anti-inflammatory				
Omega-3 essential fatty acids		→	→	→
Corticosteroid			→	→
Cyclosporine			→	→
Secretagogue			→	→
Punctal plugs			→	→
Autologous serum			→	→

[a] Activity: prolonged reading, videodisplay use, airline travel, and so forth.

secretagogue, Rebamipide (Otsuka/Novartis, Hanover, New Jersey), which seems to stimulate mucin production and has been reported from Phase II trials to reduce ocular surface staining, is well tolerated.[70] Yet another topical secretagogue being tested in Phase II trials is ecabet (Ista Pharmaceuticals, Irvine, California).

Hormone Therapy

Considering the strong laboratory evidence associating decreased androgen levels with lacrimal gland inflammation and lacrimal insufficiency, it has been suggested that androgen supplementation could be a possible therapeutic option for dry eye disease.[10,11] Epidemiologic evidence suggests that systemic estrogen-only supplementation not only does not improve symptoms of dry eye, but may aggravate symptoms of ocular irritation.[71] There is, however, accumulating evidence that topical estrogen may be a viable treatment for dry eye because of a beneficial effect on ocular surface epithelial cells (iDestrin estradiol, Nascent Pharmaceuticals, Honolulu, Hawaii). Systemic therapy with a combination of estrogen and androgen (Estratest, Solvay, Marietta, Georgia) has been associated with improvement of symptoms of dry eye in a small retrospective study.[72] Clinical trials evaluating topical testosterone applications to the ocular surface or the eyelid are in phase II trials (C. O'Connor, unpublished date, 2006). Future clinical trials are needed to prove both benefit and safety.

SUMMARY

The Sjögren's syndrome patient with dry eye disease should be evaluated with respect to the severity of their symptoms and signs, including xerostomia and keratoconjunctivitis sicca. Therapy can be guided by the severity of the disease as characterized in **Table 2**, by symptoms and signs (see **Fig. 3**), and according to the algorithm depicted in **Table 3**.

In episodic dry eye disease without significant dry mouth symptoms, use of lubricants and tear-stabilizing topical drops can be coupled with education of the patient about the need to limit long sessions on video display terminals or prolonged reading. In mild but symptomatic dry eye disease, in addition to topical lubricants, there should be evaluation of the lid margins to exclude or treat intercurrent blepharitis. Persistent symptoms despite such treatment should prompt moving to the next step in the severity scale with dietary supplementation by omega-3 essential fatty acids.

In moderately symptomatic dry eye disease, in addition to topical lubricants and omega-3 supplementation, the use of topical cyclosporine emulsion should be considered, possibly with a short course of topical steroid to improve acceptance of the cyclosporine and to speed resolution of inflammation. If dry mouth is also significantly symptomatic, an oral secretagogue (pilocarpine or cevimeline) can be added.

In severe disease topical cyclosporine emulsion concurrent with a short course of topical corticosteroid should be instituted in addition to lubricants and dietary supplementation. The presence of filaments on the corneal surface may justify the use of topical mucolytics (formulated 10% acetylcysteine three times daily). Once inflammation is controlled, punctal plug placement is also an option. In recalcitrant cases where all else has failed, use of topical autologous serum can be considered.

REFERENCES

1. DEWS Group. The report of the international dry eye workshop. Ocul Surf 2007; 5(2):1–204.
2. Report of the international dry eye workshop. Definition and classification of dry eye. Ocul Surf 2007;5:75–92.
3. Lemp MA. Report of the National Eye Institute/Industry Workshop on clinical trials in dry eye. CLAO J 1995;21:221–32.
4. Report of the international dry eye workshop. Management and therapy of dry eye disease. Ocul Surf 2007;5:163–78, therapy dews.
5. van Bijsterveld OP, Mackor AJ. Sjögren's syndrome and tear function parameters. Clin Exp Rheumatol 1989;7:151–4.
6. Strickland RW, Tesar JT, Berne BH, et al. The frequency of sicca syndrome in an elderly female population. J Rheumatol 1987;14:766–71.
7. Moss SE, Klein R, Klein BE. Incidence of dry eye in an older population. Arch Ophthalmol 2004;122:369–73.
8. Schein OD, Munoz B, Tielsch JM, et al. Prevalence of dry eye among the elderly. Am J Ophthalmol 1997;124:723–8.
9. Schaumberg DA, Sullivan DA, Buring JE, et al. Prevalence of dry eye syndrome among US women. Am J Ophthalmol 2003;136:318–26.
10. Sullivan DA. Sex hormones and Sjögren's syndrome. J Rheumatol 1997;24: 17–32.
11. Sullivan DA, Belanger A, Cermak JM, et al. Are women with Sjögren's syndrome androgen deficient? Invest Ophthalmol Vis Sci 2000;41:S276.
12. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol 2000;118:1264–8.

13. Chia EM, Mitchell P, Rochtchina E, et al. Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study. Clin Experiment Ophthalmol 2003;31:229–32.
14. Hom M, De Land P. Prevalence and severity of symptomatic dry eyes in Hispanics. Optom Vis Sci 2005;82:206–8.
15. Lee AJ, Lee J, Saw SM, et al. Prevalence and risk factors associated with dry eye symptoms: a population based study in Indonesia. Br J Ophthalmol 2002;86: 1347–51.
16. Lin PY, Tsai SY, Cheng CY, et al. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. Ophthalmology 2003;110:1096–101.
17. State-of-the-art management of chronic dry eye. A growing public health concern. Clinician 2006;24:1–19.
18. Gilbard JP, Farris RL. Tear osmolarity and ocular surface disease in keratoconjunctivitis sicca. Arch Ophthalmol 1979;97:1642–6.
19. Gilbard JP, Carter JB, Sang DN, et al. Morphologic effect of hyperosmolarity on rabbit corneal epithelium. Ophthalmology 1984;91:1205–12.
20. Luo L, Li D, Corrales RM, et al. Hyperosmolar saline is a proinflammatory stress on the mouse ocular surface. Eye Contact Lens 2005;31:186–93.
21. Stern ME, Gao J, Schwalb TA, et al. Conjunctival T-cell subpopulations in Sjögren's and non-Sjögren's patients with dry eye. Invest Ophthalmol Vis Sci 2002; 43:2609–14.
22. Brignole F, Pisella PJ, Goldschild M, et al. Flow cytometric analysis of inflammatory markers in conjunctival epithelial cells of patients with dry eyes. Invest Ophthalmol Vis Sci 2000;41:1356–63.
23. Dursun D, Wang M, Monroy D, et al. Experimentally induced dry eye produces ocular surface inflammation and epithelial disease. Adv Exp Med Biol 2002; 506:647–55.
24. Pflugfelder SC, Jones D, Ji Z, et al. Altered cytokine balance in the tear fluid and conjunctiva of patients with Sjögren's syndrome keratoconjunctivitis sicca. Curr Eye Res 1999;19:201–11.
25. Luo L, Li DQ, Doshi A, et al. Experimental dry eye stimulates production of inflammatory cytokines and MMP-9 and activates MAPK signalling pathways on the ocular surface. Invest Ophthalmol Vis Sci 2004;45:4293–301.
26. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren's syndrome. Ophthalmology 1999;106:811–6.
27. Pflugfelder SC, Maskin SL, Anderson B, et al. A randomized, double-masked, placebo-controlled, multicenter comparison of loteprednol etabonate ophthalmic suspension, 0.5%, and placebo for treatment of keratoconjunctivitis sicca in patients with delayed tear clearance. Am J Ophthalmol 2004;138:444–57.
28. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin a ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The Cyclosporin A Phase 2 Study Group. Ophthalmology 2000;107:967–74.
29. Sall K, Stevenson OD, Mundorf TK, et al. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. Ophthalmology 2000;107: 631–9.
30. Kunert KS, Tisdale AS, Stern ME, et al. Analysis of topical cyclosporine treatment of patients with dry eye syndrome: effect on conjunctival lymphocytes. Arch Ophthalmol 2000;118:1489–96.

31. Sjogren HSC. Zur kenntnis der keratoconjunctivitis sicca (Keratitis filiformis bei Hypofunktion der Tranendrusen). Acta Ophthalmol (Kbh) 1933;(Supp2):1–151.
32. Stern ME, Beuerman RW, Fox RI, et al. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. Cornea 1998;17:584–9.
33. Stern ME, Pflugfelder SC. Inflammation in dry eye. Ocul Surf 2004;2:124–30.
34. Shimazaki J, Goto E, Ono M, et al. Meibomian gland dysfunction in patients with Sjogren syndrome. Ophthalmology 1998;105:1485–8.
35. Altinors DD, Akca S, Akova YA, et al. Smoking associated with damage to the lipid layer of the ocular surface. Am J Ophthalmol 2006;141:1016–21.
36. Schlote T, Kadner G, Freudenthaler N. Marked reduction and distinct patterns of eye blinking in patients with moderately dry eyes during video display terminal use. Graefes Arch Clin Exp Ophthalmol 2004;242:306–12.
37. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea 2006;25:900–7.
38. Murube J, Paterson A, Murube E. Classification of artificial tears. I: composition and properties. Adv Exp Med Biol 1998;438:693–704.
39. Murube J, Murube A, Zhuo C. Classification of artificial tears, II: additives and commercial formulas. Adv Exp Med Biol 1998;438:705–15.
40. Gilbard JP. Human tear film electrolyte concentrations in health and dry-eye disease. Int Ophthalmol Clin 1994;34(1):27–36.
41. Gilbard JP, Rossi SR. An electrolyte-based solution that increases corneal glycogen and conjunctival goblet cell density in a rabbit model for keratoconjunctivitis sicca. Ophthalmology 1992;99:600–4.
42. Holly FJ, Lamberts DW. Effect of nonisotonic solutions on tear film osmolality. Invest Ophthalmol Vis Sci 1981;20:236–45.
43. Christensen MT, Cohen S, Rinehart J, et al. Clinical evaluation of an HP-guar gellable lubricant eye drop for the relief of dryness of the eye. Curr Eye Res 2004;28:55–62.
44. Di Pascuale MA, Goto E, Tseng SC. Sequential changes of lipid tear film after the instillation of a single drop of a new emulsion eye drop in dry eye patients. Ophthalmology 2004;111:783–91.
45. Korb DR, Scaffidi RC, Greiner JV, et al. The effect of two novel lubricant eye drops on tear film lipid layer thickness in subjects with dry eye symptoms. Optom Vis Sci 2005;82:594–601.
46. Yancey PH, Clark ME, Hand SC, et al. Living with water stress: evolution of osmolyte systems. Science 1982;217(4566):1214–22.
47. Yancey PH. Organic osmolytes as compatible, metabolic and counteracting cryoprotectants in high osmolarity and other stresses. J Exp Biol 2005;208:2819–30.
48. Barber LD, Pflugfelder SC, Tauber J, et al. Phase 3 safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. Ophthalmology 2005;112(10):1790–4.
49. Small DS, Acheampong A, Reis B, et al. Blood concentrations of cyclosporine a during long-term treatment with cyclosporine a ophthalmic emulsions in patients with moderate to severe dry eye disease. J Ocul Pharmacol Ther 2002;18(5):411–8.
50. Tang-Liu DD, Acheampong A. Ocular pharmacokinetics and safety of ciclosporin, a novel topical treatment for dry eye. Clin Pharmacokinet 2005;44:247–61.
51. Hyon JY, Lee YJ, Yun PY. Management of ocular surface inflammation in Sjögren syndrome. Cornea 2007;26(9 Suppl 1):S13–5.
52. Strong B, Farley W, Stern ME, et al. Topical cyclosporine inhibits conjunctival epithelial apoptosis in experimental murine keratoconjunctivitis sicca. Cornea 2005;24(1):80–5.

53. Kunert KS, Tisdale AS, Gipson IK. Goblet cell numbers and epithelial proliferation in the conjunctiva of patients with dry eye syndrome treated with cyclosporine. Arch Ophthalmol 2002;120:330–7.
54. Nelson JD. Impression cytology. Cornea 1988;7(1):71–81.
55. Zhao H, Jumblatt JE, Wood TO, et al. Quantification of MUC5AC protein in human tears. Cornea 2001;20:873–7.
56. Horrobin DF. Essential fatty acid and prostaglandin metabolism in Sjögren's syndrome, systemic sclerosis, and rheumatoid arthritis. Scand J Rheumatol Suppl 1986;61:242–5.
57. Miljanovic B, Trivedi KA, Dana MR, et al. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. Am J Clin Nutr 2005;82:887–93.
58. Barabino S, Rolando M, Camicione P, et al. Systemic linoleic and gamma-linolenic acid therapy in dry eye syndrome with an inflammatory component. Cornea 2003;22:97–101.
59. Rashid S, Jin Y, Ecoiffier T, et al. Topical omega-3 and omega-6 fatty acids for treatment of dry eye. Arch Ophthalmol 2008;126:219–25.
60. Nelson JD, Friedlander M, Yeatts RP, et al. Oral pilocarpine for symptomatic relief of keratoconjunctivitis sicca in patients with Sjögren's syndrome. The MGI Pharma Sjögren's Syndrome Study Group. Adv Exp Med Biol 1998;438:979–83.
61. Mathers WD, Dolney AM. Objective demonstration of tear stimulation with oral pilocarpine in dry eye patients. Invest Ophthalmol Vis Sci 2000;41:s60.
62. Vivino FB, Al-Hashimi I, Khan Z, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjogren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group. Arch Intern Med 1999;159:174–81.
63. Petrone D, Condemi JJ, Fife R, et al. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum 2002;46:748–54.
64. Fox RI, Chan R, Michelson JB, et al. Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca. Arthritis Rheum 1984;27:459–61.
65. Tsubota K, Goto E, Fujita H, et al. Treatment of dry eye by autologous serum application in Sjögren's syndrome. Br J Ophthalmol 1999;83:390–5.
66. Tsubota K, Higuchi A. Serum application for treatment of ocular surface disease. Int Ophthalmol Clin 2000;40:113–22.
67. Pflugfelder SC. Is autologous serum a tonic for the ailing corneal epithelium? Am J Ophthalmol 2006;142:316–7.
68. Li Y, Kuang K, Yerxa B, et al. Rabbit conjunctival epithelium transports fluid, and P2Y2(2) receptor agonists stimulate Cl (–) and fluid secretion. Am J Physiol Cell Physiol 2001;281:C595–602.
69. Tauber J, Davitt WF, Bokosky JE, et al. Double-masked, placebo-controlled safety and efficacy trial of diquafosol tetrasodium (INS365) ophthalmic solution for the treatment of dry eye. Cornea 2004;23:784–92.
70. Donshik PC, et al. Association for Research in Vision and Ophthalmology Annual Meeting. Fort Lauderdale (FL), April 30–May 4, 2006.
71. Schaumberg DA, Buring JE, Sullivan DA, et al. Hormone replacement therapy and dry eye syndrome. JAMA 2001;286:2114–9.
72. Scott G, Yiu SC, Wasilewski D, et al. Combined esterified estrogen and methyltestosterone treatment for dry eye syndrome in postmenopausal women. Am J Ophthalmol 2005;139:1109–10.

Optimizing Dry Mouth Treatment for Individuals with Sjögren's Syndrome

Ava J. Wu, DDS

KEYWORDS

• Sjögren's syndrome • Xerostomia • Salivary dysfunction
• Artificial saliva • Remineralization

A hallmark of the oral component of Sjögren's syndrome (SS) is the complaint of dry mouth thought to be secondary to dysfunction of the salivary glands. In fact, although most individuals ultimately diagnosed with SS do have severe salivary dysfunction, many of these individuals have salivary function within the normal range.[1] Thus, for optimized treatment of individuals who have salivary dysfunction, it becomes important to determine how a patient's salivary glands function under unstimulated and stimulated conditions, to examine the quality of the saliva, and to assess the oral cavity for the sequelae of salivary gland dysfunction. Oral signs suggestive of salivary dysfunction include:

Dental caries (incisal and cervical)
Dental erosion
Sticking and smacking sounds of mucosa sticking to teeth during speech
Dry appearance to the oral mucosa
Absence of saliva pooling in the floor of the mouth
Absence of expressible saliva from the major salivary gland orifices
Depapillation of tongue
Erythematous candidiasis

Measurement of unstimulated salivary function offers insight into how the individual is functioning under basal conditions and is representative of the level that the salivary glands are functioning for most of the day. Measurement of stimulated salivary function gives an indication of the capacity of the gland to respond to an external stimulus such as food, gum, talking, or the use of a muscarinic agonist (ie, cevimeline hydrochloride, pilocarpine hydrochloride). If a patient has an extremely low salivary flow

Sjögren's Syndrome Clinic, University of California, San Francisco, 513 Parnassus Avenue, Room C646, CA 94143, USA
E-mail address: ava.wu@ucsf.edu

Rheum Dis Clin N Am 34 (2008) 1001–1010
doi:10.1016/j.rdc.2008.08.013 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

rate under resting conditions, are the salivary glands able to mobilize under stimulated conditions? This information helps to stratify the patient appropriately into a population that is at risk for the sequelae of salivary dysfunction, and to predict how he or she will respond to specific therapeutic strategies, enabling personalization of a preventative regimen.

Saliva has several important functions, including: buffering; provision of antimicrobial proteins; protection, lubrication, and repair of oral mucosal tissue; formation and maintenance of the protective dental pellicle; initiation of enzymatic digestion of ingested food; and facilitating access of food to taste buds. The loss of the ability to produce physiologically relevant amounts of saliva includes the sensation of dry mouth, dental caries, oral infections, difficulty swallowing, intolerance to spicy or acidic foods, and altered speech. In this article, the optimal management of individuals who complain of dry mouth is directed primarily at the following areas: (1) assessment of status of the oral mucosa; (2) assessment of salivary gland function; and (3) management of dental caries, xerostomia, and oral infections.

ASSESSMENT OF ORAL MUCOSA

The face is observed for fullness suggestive of salivary gland enlargement. Speech is assessed for the smacking sound of the dry oral mucosa sticking to the teeth. The lips are observed for dryness, fissuring, erythema, ulceration, and swelling. The mouth is examined starting with the labial mucosa, the buccal mucosa, the hard/soft palate, the gingiva, the tongue, and the floor of mouth. A piece of gauze is used to dry the floor of the mouth to determine whether pooling occurs as saliva exits the submandibular/sublingual glands. Bimanual palpation of the submandibular/sublingual glands is used to determine if swelling is present. Saliva is assessed as it is expressed from the right and left parotid papillae, where it exits from Stenson's duct into the oral cavity. The quality of the saliva is noted as clear, cloudy, or thickened, along with the presence or absence of pain/sensitivity with the saliva milking process. Typically saliva exiting the parotid glands will disperse immediately. A hanging drop indicates increased viscosity of the saliva. The body of the parotid gland sits on top of the masseter muscle and may be difficult to palpate. The patient may be asked to clench his or her teeth to tense the masseter, allowing delineation between the masseter and the parotid gland. The nature of the enlargement (from protocols developed for the Sjögren's International Collaborative Clinical Alliance; http://sicca.ucsf.edu) can be described as soft (texture of tofu), firm (like an orange), hard (like an apple), nodular (one or more defined masses within the gland that are firm or hard), diffuse (presence of enlargement throughout the glands), or fluctuant (fluid-filled, as in a cyst). The presence or absence of tenderness should be noted. The most common soft tissue oral lesion observed in patients who have SS is an erythematous candidal infection, which will be addressed in further detail below. The temporomandibular joint (TMJ) is assessed for clicking, popping, crepitus, and asymmetry. The possibility of pathology in the TMJ has implications regarding the repetitive action of gum chewing to stimulate saliva. The teeth are examined for the presence of active, recurrent, and incipient caries on the cervical and incisal edges of teeth and unexplained incisal or cervical wear suggestive of a chemical erosive process. The possibility of chemical erosion of the teeth is considered, because there is some evidence that individuals who have salivary dysfunction may not be able to neutralize endogenous/exogenous acids efficiently.[2,3]

ASSESSMENT OF SALIVARY GLAND FUNCTION

Determination of a salivary flow rate or evaluation of salivary function is intrinsically a crude measurement that is probably best for identifying those individuals who are at either extreme of salivary production, that is either too little or plenty of saliva. This determination may be done by salivary scintigraphy or by the cost- and time-efficient method of spitting into a preweighed tube according to a specific protocol (**Boxes 1** and **2**). To date, researchers have been unable to precisely or numerically define what constitutes a normal salivary flow rate. What is known is that an individual's whole salivary flow rate must drop by approximately 50% of his or her baseline flow before he or she will begin to complain of oral dryness.[4,5] In addition, those who have little or no salivary function suggestive of the oral component of SS have been defined in the American–European Consensus criteria as an unstimulated whole salivary flow rate less than 0.100 mL/min.[6] This rate is being tested using a larger population that is part of the Sjögren's International Collaborative Clinical Alliance (http://sicca.ucsf.edu).

A reduced stimulated whole salivary flow rate has been estimated to be from 0.5 mL/min to 0.7 mL/min.[7] Again, cut-off points determined for stimulated whole saliva are best at identifying those individuals who are totally unable to produce measurable amounts of stimulated saliva (ie, may not respond well to strategies designed to increase salivary flow) and those individuals who cannot produce any unstimulated saliva, but are able to produce saliva when stimulated (ie, likely to respond well to methods used to stimulate saliva). A commercial kit, GC Saliva Check (GC America, Alsip, Illinois) is available to facilitate the procedure.

In the eye, the use of omega fatty acids may change the quality of tears[8] and may improve clinical indices. including Schirmer I test, tear break-up time. and van Bjisterveld score.[9] A clinical trial is underway to examine the effect(s) of omega fatty acids on salivary flow. Linseed oil (ie, flaxseed oil/Omega 3) and evening primrose oil (omega 6) have been examined as oral moisturizing agents with mixed results.[9–11]

MANAGEMENT OF DENTAL CARIES

A seminal study showed that for individuals who have compromised salivary function, excellent oral hygiene alone is insufficient to prevent rapidly progressive dental decay.[12] The use of topical fluoride and diet counseling was critical for caries prevention.

Box 1
Protocol for determination of unstimulated whole salivary flow rate

Unstimulated whole saliva collection measures saliva production under resting or basal conditions. The subject should not have had anything to eat or drink for 90 minutes before the procedure. The use of a parasympathomimetic should be discontinued for 12 hours before the procedure, and the use of artificial salivas should be stopped 3 hours prior. During the collection procedure, the subject is instructed to minimize actions that can stimulate saliva (talking, increased orofacial movement) and should not swallow. At time "0," any saliva present in the mouth is cleared by swallowing. For the subsequent 5 minutes, any saliva collected in the mouth is emptied into a preweighed tube every minute (ie, five times). This collecting tube then is weighed to determine a postcollection weight. The difference between the pre- and postcollection weight is determined, and this represents the unstimulated whole saliva production for 5 minutes. To convert to a volume of saliva from the weight of saliva, an assumption is made that saliva is similar to water, where 1 g of water/saliva at 4°C equals 1 mL of saliva/water. Less than 0.100 mL/min is considered a reduced unstimulated salivary flow rate.[6]

Adapted from Protocols developed for the Sjögren's International Collaborative Clinical Alliance (http://sicca.ucsf.edu); with permission.

Box 2
Protocol for determination of a stimulated whole salivary flow rate

A stimulated whole salivary flow rate may be determined by using a preweighed tube and small piece of paraffin or unflavored chewing gum. The patient chews on the preweighed paraffin in a precise, timed manner for 5 minutes, and the saliva is emptied into the preweighed graduated tube. At the end of the collection period, the saliva-soaked paraffin is placed into the preweighed tube containing the collected saliva. The weight of saliva + paraffin is divided by total minutes collected to determine the salivary flow (mL/min).

A reduced stimulated whole salivary flow rate would be less than 0.5 mL/min to 0.7 mL/min.[7]

Caries is an oral disease that can be exacerbated by salivary dysfunction. Therefore, treatment of this oral disease should address prevention and management. Important to this process are:

Caries risk assessment
Diet assessment
Early detection and prevention of caries
Chemoprophylaxis to decrease the bacteria thought to contribute to the decay process
Use of new dental procedures allowing the practice of minimally invasive dentistry
Increasing the amount of saliva in the mouth
Managing oral mucosal infections

Caries risk assessment can be determined from the oral examination looking for clinical signs of hyposalivation, measurement of salivary production, presence and number of active caries lesions, amount of plaque, quality of diet, frequency of ingestion and duration of exposure to sugar and fermentable carbohydrates, use of xerostomic medication, and clinical judgment. Specific protocols have been developed for caries risk assessment (Caries Management by Risk Assessment, CAMBRA),[13,14] where an individual may be triaged into low-, moderate-, high-, and extremely high-risk categories.

There are some very limited clinical data showing that individuals who have salivary dysfunction are not be able to raise intraoral pH back into the neutral range after an acidic challenge as quickly as those individuals who can produce saliva.[2,3] A critical pH has been defined at 4.5 to 5.5 for the enamel tooth surface and at 6.2 to 6.4 for the exposed root surface. Below this critical pH, oral conditions favor demineralization or promotion of the caries process on the tooth surface. Progression of dental decay may be faster on the root surface in an oral environment that tends toward acidity. Saliva is the oral buffering agent, so the inability to produce saliva under resting/basal conditions or the inability to increase production under stimulated conditions may result in a compromised ability to buffer acid from plaque and exogenous sources. The management goal is therefore to shift the intraoral pH away from conditions that favor demineralization toward an environment that favors remineralization of the tooth surface. Carbonated beverages, juices, or waters (with additives) are examples of an exogenous acid that can have a pH ranging from 2.5 to 4.[15–18] A baking soda rinse (2 teaspoons in a small 12 to 16 oz bottle of water) has been proposed for use several times of day to neutralize intraoral pH.[14,19] Baking soda gums are also available.[20,21] Clinical evidence supporting the use of bicarbonate to directly interfere with the caries process in those who have normal or reduced ability to salivate is lacking. Salivary buffering capacity may be assessed using commercially available kits (Dentobuff Strips, Orion Diagnostics, Esposo, Finland; GC Saliva Check, GC America).

The use of sugar-free gum and candies has been recommended to increase salivary flow. Again, this technique is most effective for those individuals who have some stimulated salivary function. Xylitol is thought to have an indirect role in reducing the population of bacteria that cause decay, inhibiting demineralization and promoting remineralization, and inhibiting plaque formation.[22,23] Xylitol is taken up by oral bacteria and either metabolized slowly or not at all, and it can result in a shift in the intraoral bacterial population to one that is less cariogenic. The clinical evidence for xylitol having a direct cariostatic effect is mixed.[24,25] The precise amount of xylitol to prevent caries in vivo has not been defined precisely.[22] The adjunctive use of a xylitol- containing gum or candy four to five times per day for 5 minutes after meals and snacks is recommended.[14,25] The use of chewing gum should be judicious or avoided in those who have pathology of the temporomandibular joint.

Commercial kits are available to monitor levels of caries causing bacteria in the mouth (Dentocult strips, Orion Diagnostics). To assist in management of these bacteria and their effects, the use of chemoprophlyactics is becoming more common. Short-term consumption of xylitol is associated with a decrease in the caries-causing bacteria *Streptococcus mutans* levels, and long-term consumption is associated with a shift in the bacterial population to one that is less adherent to the tooth surface. Baking soda has antibacterial properties and has the ability to neutralize acid (Arm and Hammer Dental Care Toothpaste and Baking Soda Gum). A 0.12% chlorhexidine gluconate mouth rinse may be used for 1 minute daily at bedtime for 1 week each month. Individuals who have severe dry mouth may be sensitive to the alcohol in this rinse. An alcohol-free version of the chlorhexidine rinse is available but limited in its distribution. Chlorhexidine gels and varnishes are not available In the United States. Chlorhexidine can bind to fluoride, so they should not be used concurrently; alternatively, it may be used at a separate time.

Diet assessment should address eating habits beyond the role of sugar in caries promotion.[24] The frequency of ingestion of fermentable carbohydrates and exogenous acids (ie, carbonated beverages, wine, citrus) and the duration of exposure can play a role in caries promotion. Strategies to minimize the intraoral effects of these foods and beverages may be initiated.

Early detection of caries is critical in that it is known that an early, noncavitated (white spot, **Fig. 1**) lesion can be reversed or arrested from progressing by chemical means (fluoride) rather than by restorative means. Thus early detection equals prevention.

PROMOTION OF REMINERALIZATION AND REVERSAL OF THE DEMINERALIZATION PROCESS

The early carious lesion can be reversed by the remineralization process. The use of fluoride is critical for the process of remineralization. The action of fluoride is considered to be topical, promoting remineralization and inhibiting demineralization of teeth. Additionally, it may inhibit plaque bacteria. There are many brands and types of topical fluorides available that can be professionally or self-applied. For those at lowest risk, a 0.05% sodium fluoride rinse (ACT rinse, Fuoriguard, Carifree Maintenance Rinse) is available over the counter and may be used for 1 to 2 minutes daily. Higher-level fluoride rinses, gels, and dentifrices are available by prescription. 1.23% acidulated phosphate gel (many brands) is not very well tolerated by those who have severe salivary gland dysfunction because of mucosal sensitivity. The author usually prescribes a 1.1% neutral sodium fluoride dentifrice (Prevident 5000, Control Rx Multi 1.1% NaF dentifrice with xylitol) or gel. The neutral gel can be applied in a custom tray for 5 to 10 minutes once daily and seems to be tolerated well by those who

Fig. 1. 48-year-old male previously diagnosed with SS. Unstimulated whole salivary flow rate is reduced at less than 0.1 mL/min. The stimulated parotid salivary flow rate is on the low side of normal. Incipient caries or white spot demineralized lesions are noted on the cervical area of the maxlilary and mandibular cuspids, bicuspids and molars (arrows only indicate mandibular lesions). The teeth were treated with 5% sodium fluoride varnish. The patient will initiate a daily regimen of 1.5% NaF dentifrice, except when using a chlorhexidine rinse for 1 week out of a month, and will chew gum or apply a paste with recaldent to deliver calcium and phosphate to the tooth surface. The patient was counseled on diet and management of intraoral pH. He elected to continue to use water as his wetting agent of choice and not to use a muscarinic agonist to stimulate salivary flow.

have sensitive mucosa. For greater compliance, the neutral fluoride can be prescribed as a toothpaste/toothpaste, where application can be done simultaneous with tooth brushing. After application of the fluoride, the interproximal dental areas should be flossed to deliver the medicament to these generally inaccessible areas. 5% sodium fluoride varnish (Duraphat, Durafluor, Cavity Shield) or 0.1% difluorsilane varnish (Fluor Protector, Ivoclar, Viadent) may be applied professionally two to four times per year to the most caries- susceptible areas of the mouth (exposed root surfaces, around crown margins, and at incisal edges). This product is US Food and Drug Administration (FDA)-approved as an anticaries agent for children. This product allows extended release of the active ingredient with no measurable systemic levels, and it may be applied directly to potential problem areas of the tooth.

Salivary calcium and phosphate interacts with the available salivary fluoride to enhance the remineralization process. Sialochemistry studies show that patients who have SS may have decreased salivary phosphate levels with no change in calcium levels.[26] Remineralizing agents that deliver calcium and phosphate to the tooth surface are becoming available in the United States. Prospec MI paste uses Recaldent, a milk-derived protein to deliver calcium and phosphate. This product can be applied professionally with a prophy cup, in a tray, or be used at home under professional supervision. Recaldent chewing gum may be used two to six times daily. Short-term studies have shown that temporarily increasing calcium and phosphate levels in saliva may be beneficial in helping those who have salivary dysfunction to more efficiently use fluoride. There is no consensus, however, on how often or how much calcium phosphate should be delivered for maximum effectiveness,[15] and there have been no clinical trails specifically testing the effectiveness of these newer remineralizing agents in patients who have salivary dysfunction.

Minimally invasive dentistry (MID) is a concept that the profession has been shifting toward in the past decade.[27–29] This shift has been facilitated by the development of

new technologies and materials. The goal of this philosophy is to conserve healthy tooth structure and to realize that permanent restorations usually will need replacement in the future and that there is a restoration cycle that can lead to larger and larger restorations, tooth fracture, endodontic treatment, and eventually extraction of the tooth. Theoretically, this restoration cycle can be accelerated for individuals who have salivary dysfunction. The goal of MID is to interrupt and slow this restoration cycle. Consequently, dental caries is treated like an infectious disease, and strategies to prevent the decay process may be initiated. Newly developed dental materials allow the dentist to place smaller, conservative restorations to preserve existing tooth structure and to repair existing restorations with fluoride-releasing materials rather than to replace it with something slightly larger. Subgingival margins are difficult to clean, most susceptible to recurrent decay, and least accessible to cleansing and remineralization/antimicrobial strategies. Subgingival margins on a restoration are placed below the gum line and are not always avoidable in the interest of aesthetics. Supragingival, above the gum line, margins are preferred. If necessary, full coverage crowns should not be placed unless caries activity is controlled.

Increasing the amount of saliva in the mouth may be achieved in those individuals who have functioning salivary glands by means of the use of sugar-free hard candies or lozenges (Salive), sugar-free chewing gum, or by the use of a muscarinic agonist. A xylitol- containing gum or candy may have additional clinical benefit (Xylichew, Spry, TheraGum,). Pilocarpine tablets, Cevimeline capsules, or Bethanachol may be prescribed to increase saliva production. These medications are contraindicated in those who are pregnant or have a history of uncontrolled asthma, gastrointestinal ulcer, acute iritis or narrow angle glaucoma, and they may not be suitable for those who have unstable cardiovascular disease. Some individuals decide to discontinue the prescribed muscarinic agonist because of intolerable adverse effects, including sweating. In these cases, it is possible to titrate the medication (ie, pilocarpine, by cutting the 5 mg or 7.5 mg pill to a final dose of 2.5 to 3.75 mg three times daily, or dissolving one half capsule of cevimeline in 1 tablespoon of water) to maximize the sensation of increased saliva while minimizing systemic adverse effects. A single paper noted that cevimeline is highly soluble in water and suggested that a very short topical effect could be obtained by means of a rinse-and-spit regimen, avoiding systemic absorption of the medication.[30] Other individuals benefit by switching to an alternative medication (ie, bethanechol or pilocarpine or cevimeline).[31]

Artificial salivas are available and are primarily palliative. Some of these products will have additives aimed at stimulating saliva or providing beneficial proteins, enzymes, or ions. Some patients depend on these products extensively. Others find these products not to their taste, and prefer water as a wetting agent. In any case, patients are advised to try different products to determine if there is one that they like. These products are useful to get very dry patients through difficult periods (telephone conversations, going to sleep, and social interactions). Patients are advised to make sure the artificial saliva is applied to the hard palate, buccal mucosa, and inner lips.[32]

Oral Infections in patients who have salivary dysfunction tend to be primarily mucosal erythematous fungal infections, or less frequently infection of the salivary glands. Clinically, this type of fungal presents as generalized or localized patchy areas of erythema on the tongue, buccal mucosa, palate, lips, and corners of the lips. The erythema almost invariably is associated with the sensation of burning and sensitivity to spicy/acidic foods. If the infection is on the tongue, depapillation (bald tongue) may be observed. With treatment, the burning sensation, depapillation of tongue, and taste alterations will resolve. If the burning sensation does not resolve with treatment, and there is an absence erythema at the site, then the presence of burning mouth

syndrome[33] should be considered. The treatment of choice for an oral fungal infection in the author's clinic is topical Nystatin Vaginal tablets (10^5 units/tablet), because there is no fermentable carbohydrate in the carrier. The patient is instructed to suck on the tablet three to four times a day for 7 to 10 days. For those who have severe salivary dysfunction, small sips of water may be necessary to facilitate dissolution of the tablet. Most antifungal preparations for oral use contain sugar to increase palatability. If a sugar-containing oral preparation is used, the patient should be informed to not use the medication immediately before bed without a thorough tooth brushing. A systemic medication may be used, but there is some concern that that the salivary level of the medication may not be sufficient in those who have the most severe salivary dysfunction.[34] Thus, the patient should be informed that if there is not significant resolution in 7 to 10 days with the systemic medication, he or she will be switched to a topical oral antifungal. A fungal infection of the lip is treated with either a nystatin crème or nystatin crème with triamcinolone acetonide (ie, Mycolog II). The presence of a denture adds complexity to the treatment process, as it will need to be treated also. The denture may be soaked overnight in 0.2% chlorhexidine or a dilute bleach solution. Please note that chlorhexidine and nystatin should not be used together, as chlorhexidine–nystatin complexes may be formed, inactivating both compounds.[35] The patient may sprinkle a fine layer of nystatin powder for oral suspension onto moistened surface of the wet denture and wear through the day. The patient should be instructed regarding the possibility of cross-contamination with lipsticks and toothbrushes.

SUMMARY

The optimal management of the oral component of SS can contribute to the SS patient's overall quality of life.[36] Critical to this process is patient education based on rational assessment of the patient's complaint, functional ability of the salivary glands, and the status of the oral mucosa and dentition. The patient should be educated on the spectrum of potential problems and of the different levels of available strategies to manage a specific oral complaint and to increase oral comfort. These strategies may include some combination of:

A gustatory or pharmacologic method to increase salivary flow
Antibacterial mouthwashes
Topical fluoride in the form of a dentifrice, mouth rinse or varnish
Xylitol
An oral buffering product
Artificial saliva/moisturizing spray or rinse
A remineralizing product to deliver calcium and phosphate ions to the tooth surface

In the event of active caries, the patient will have an understanding of the practice of MID. Many of the new strategies and products described in this article have been detailed as part of a series of guidelines known as CAMBRA or[14,19,36] (www.cdafoundation.org/journal). These guidelines provide a framework for patient management, future product development, and design of clinical trials, and certainly will evolve as new products and the results of clinical trials and experience become available.

REFERENCES

1. Atkinson JC, Travis WD, Pillemer SR, et al. Major salivary gland function in primary Sjögren's syndrome and its relationship to clinical features. J Rheumatol 1990; 17(3):318–22.

2. Featherstone JD. Prevention and reversal of dental caries: role of low-level fluoride. Community Dent Oral Epidemiol 1999;27(1):31–40.
3. Featherstone JD. The science and practice of caries prevention. J Am Dent Assoc 2000;131(7):887–99.
4. Dawes C. Physiologic factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. J Dent Res 1987;66(Spec Iss):648–53.
5. Wolff MS, Kleinberg L. The effect of ammonium glycopyrrolate (Robinol)-induced xerostomia on oral mucosa wetness and flow of gingival crevicular fluid in humans. Arch Oral Biol 1999;44:97–102.
6. Vitali C, Bombardieri S, Jonsson R, et al. European Study Group on Classification Criteria for Sjögren's Syndrome: a revised version of the European criteria proposed by the American–European Consensus Group. Ann Rheum Dis 2002; 61(6):554–8.
7. Sreebny LM, Zhu WX. The use of whole saliva in the differential diagnosis of Sjögren's syndrome. Adv Dent Res 1996;10(1):17–24.
8. Aragona P, Bucolo C, Spinella R, et al. Systemic omega 6 fatty acid treatment and pge1 tear content in Sjögren's syndrome patients. Invest Ophthalmol Vis Sci 2005;46(12):4474–9.
9. Oxholm P, Manthorpe R, Prauss JU, et al. Patients with primary Sjögren's syndrome treated for two months with evening primrose oil. Scand J Rheumatol 1986;15(2):103–8.
10. Andersson G, Johansson G, Attström R, et al. Comparison of the effect of the linseed extract Salinum and a methycellulose preparation on the symptoms of dry mouth. Gerodontology 1995;12(1):12–7.
11. Johansson G, Andersson G, Edwardsson S, et al. Effects of mouth rinses with linseed extract Salinum without/with chlorhexidine on oral conditions in patients with Sjögren's syndrome. A double- blind crossover investigation. Gerodontology 2001;18(2):87–94.
12. Dreizen S, Brown LR, Daly TE, et al. Prevention of xerostomia-related dental caries in irradiated cancer patients. J Dent Res 1977;56(2):99–104.
13. Jensen L, Budenz AW, Featherstone JD, et al. Clinical protocols for caries management by risk assessment. J Calif Dent Assoc 2007;35(10):714–23.
14. Featherstone JD, Young DA, Domejean-Orliaguet S, et al. Caries risk assessment in practice for age 6 through adult. J Calif Dent Assoc 2007;35(10):703–13.
15. Wu AJ. The oral component of Sjögren's syndrome: pass the scalpel and check the water. Curr Rheumatol Rep 2003;5(4):304–10.
16. Jensdottir T, Holbrook P, Nauntofte B, et al. Immediate erosive potential of cola drinks and orange juices. J Dent Res 2006;85(3):226–30.
17. Hara AT, Zero DT. Analysis of the erosive potential of calcium-containing acidic beverages. Eur J Oral Sci 2008;116(1):60–5.
18. Spolsky VW, Black BP, Jensen L, et al. Products—old, new, and emerging. J Calif Dent Assoc 2007;35(10):724–37.
19. Igarishi K, Lee IK, Schachtele CF. Effect of chewing gum containing sodium bicarbonate on human interproximal plaque pH. J Dent Res 1998;67(3):531–5.
20. Anderson LA, Orchardson R. The effect of chewing bicarbonate-containing gum on salivary flow rate and pH in humans. Arch Oral Biol 2003;48(3):201–4.
21. Lynch H, Milgrom P. Xylitol and dental caries: an overview for clinicians. J Calif Dent Assoc 2003;31(3):205–9.
22. Ly KA, Milgrom P, Rothen M. Xylitol, sweeteners, and dental caries. Pediatr Dent 2006;28(2):154–63.

23. Burt BA, Pai S. Sugar consumption and caries risk: a systematic review. J Dent Educ 2001;65(10):1018–23.
24. Burt B. The use of sorbitol- and xylitol-sweetened chewing gum in caries control. J Am Dent Assoc 2006;137(4):190–6.
25. Kalk WW, Vissink A, Spijkervert FK, et al. Sialometry and sialochemistry: diagnostic tools for Sjögren's syndrome. Ann Rheum Dis 2001;60(12):1110–6.
26. White J, Eakle S. Rationale and treatment approach in minimally invasive dentistry. J Am Dent Assoc 2000;131:13S–9S.
27. Christensen G. The advantages of minimally invasive dentistry. J Am Dent Assoc 2005;136(11):1563–5.
28. Murdoch-Kinch C, McLean M. Minimally invasive dentistry. J Am Dent Assoc 2003;134(1):87–95.
29. Takagi Y, Kimura Y, Nakamura T. Cevimeline gargle for the treatment of xerostomia in patients with Sjögren's syndrome. Ann Rheum Dis 2004;63(6):749.
30. Chainani-Wu N, Gorsky M, Mayer P, et al. Assessment of the use of sialogogues in the clinical management of patients with xerostomia. Spec Care Dentist 2006; 26(4):168–74.
31. Dawes C. How much saliva is enough for avoidance of xerostomia? Caries Res 2004;38(3):236–40.
32. Patton LL, Siegel MA, Benoliel R, et al. Management of burning mouth syndrome: systematic review and management recommendations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(Suppl):1–13.
33. Garcia-Hermoso D, Dromer F, Improvisi L, et al. Fluconazole concentrations in saliva from AIDS patients with oropharyngeal candidiasis refractory to treatment with fluconazole. Antimicrob Agents Chemother 1995;39(3):656–60.
34. Barkvoll P, Attramadal A. Effect of nystatin and chlorhexidine gluconate on *C albicans*. Oral Surg Oral Med Oral Pathol 1989;67(3):279–81.
35. Stewart CM, Berg KM, Cha S, et al. Salivary dysfunction and quality of life in Sjögren's syndrome. J Am Dent Assoc 2008;139(3):291–9.
36. Young DA, Featherstone JDB, Roth JR. Caries management by risk assessment—a practitioner's guide. J Calif Dent Assoc 2007;35(10):679–80.

Issues Related to Clinical Trials of Oral and Biologic Disease-Modifying Agents for Sjögren's Syndrome

Steven E. Carsons, MD[a,b,*]

KEYWORDS

• Sjögren's • Clinical trials • DMARD • Biologics
• Outcome • Study design

Restoration of salivary and lacrimal function has been a major therapeutic goal in the management of Sjögren's syndrome (SS) over the past several decades. Successful efforts have focused on the development of cholinergic muscarinic agonists for oral administration culminating in Food and Drug Administration (FDA) approval of oral pilocarpine and cevimeline. The rationale for this form of therapy presupposes the existence of functionally viable glandular units capable of stimulation. Although data from randomized clinical trials have demonstrated significant increases in salivation,[1,2] there is no evidence to suggest that secretagogue therapy affects the autoimmune inflammatory process in SS. Additionally, there has been a recent increase in the number of publications documenting extraglandular involvement in primary SS. Despite the development of oral and biologic agents that have significant activity against other autoimmune disorders, including rheumatoid arthritis (RA), the spondyloarthropathies, and inflammatory bowel disease, no effective treatment has been documented for the glandular or systemic features of primary SS. This article reviews existing data on the use of disease-modifying therapy for glandular and extraglandular manifestations of primary SS and explores issues related to clinical development of disease-modifying agents for primary SS. Disease-modifying agents that have been evaluated for the treatment of SS are listed in **Box 1**.

[a] SUNY at Stony Brook School of Medicine, Stony Brook, NY, USA
[b] Division of Rheumatology, Allergy and Immunology, Winthrop University Hospital, 120 Mineola Boulevard, Suite 410, Mineola, NY 11501, USA
* Division of Rheumatology, Allergy & Immunology, Winthrop University Hospital, 120 Mineola Boulevard, Suite 410, Mineola, NY 11501.
E-mail address: Scarsons@winthrop.org

Rheum Dis Clin N Am 34 (2008) 1011–1023
doi:10.1016/j.rdc.2008.08.005 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

Box 1
Disease-modifying agents studied in clinical trials for the treatment of Sjögren's syndrome

Oral disease-modifying antirheumatic drugs (DMARDs)
- Hydroxychloroquine
- Azathioprine
- Sulfasalazine
- D-penicillamine (D-PA)
- Azathioprine
- Cyclosporin A (CycA)
- Interferon (IFN)-α

Oral corticosteroids

Agents that modify inflammatory lipids
- Nonsteroidal anti-inflammatory drugs
- Dihomo gamma-linoleic acid

Antiretroviral agents

Androgenic hormones

Biologic DMARDs
- Tumor necrosis factor (TNF)-α inhibitors
- B-cell depletion agents

CORTICOSTEROIDS

Although corticosteroids are used extensively in the treatment of autoimmune and rheumatic disorders, there is little evidence to support their use for the treatment of glandular dysfunction in SS. In a well-documented study using a double-blind placebo-controlled design, Fox and colleagues[3] treated 24 patients who had primary SS with prednisone (30 mg alternate days), piroxicam (20 mg daily), or placebo for 6 months. Entry criteria included a positive minor salivary gland biopsy demonstrating greater than 1 focus of mononuclear cells and the absence of another systemic rheumatic disease. Patients were assessed at baseline, after 6 months of therapy, and 4 months after the completion of therapy (10 months). No differences were noted in salivary flow rates as determined by individual collection from the parotid, submandibular, and sublingual glands. Focus score as determined by rebiopsy at 6 months revealed a decline only for the placebo group. Pathologic analysis of other glandular structures, including acini and ducts, showed no changes for any group. Not unexpectedly, laboratory parameters revealed a decline in the erythrocyte sedimentation rate (ESR), total IgG, and total IgA at 6 months. These improvements were no longer noted at 10 months. When cumulative visit data were analyzed, a significantly greater number of patients in the prednisone group reported subjective improvement in the amount of saliva present. Nonetheless, this group reported worsening of symptoms related to oral dryness and ocular dryness. Fewer steroid-treated patients self-reported episodes of salivary gland enlargement, increases in joint pain, and fatigue compared with the placebo or piroxicam groups. More steroid-treated patients reported increases in energy and appetite. Miyawaki and colleagues[4] conducted a 48-month prospective, open-label, pilot study

of corticosteroids in patients who had primary SS and were diagnosed according to Japanese criteria.[5] Follow-up was performed every 6 months. Twenty patients received initial treatment with prednisolone daily (15 mg) with subsequent taper to 5 to 7.5 mg per day for maintenance. Ten patients remained in the study and were tapered to a mean of 5.3 mg per day at 24 months. Only six patients completed the study at 48 months, all receiving 5 mg per day. These data revealed significant increases in saliva production as measured by the Saxon test beginning at 1 month and peaking at 3 months with an approximate doubling of salivary output. Saliva production subsequently declined but remained significantly increased compared with baseline at all time points until study termination. This study also revealed significant decreases from baseline in all serologic parameters measured, including serum IgG, IgA, IgM, anti SS-A/Ro, anti SS-B/La, and IgM rheumatoid factor (RF). Differences between the outcomes reported by Miyawaki and colleagues and by Fox and colleagues include study design (randomized double-blind versus open-label), length of follow-up, and method of measuring salivary production. The total number of patients studied was small and no patient received more than the equivalent of 15 mg of prednisolone daily. Low-dose oral corticosteroid therapy may help treat episodes of glandular swelling and seems to reduce subjective symptoms of dryness but does not seem to halt disease progression.

HYDROXYCHLOROQUINE

Hydroxychloroquine (HCQ) is used widely in the management of primary SS by rheumatologists despite a lack of evidence for sustained objective improvement in glandular function. A 2-year, double-blind, crossover trial reported by Kruize and colleagues[6] enrolled 19 patients who were randomized to HCQ for 1 year followed by placebo for 1 year or placebo for 1 year followed by 12 months of HCQ. All patients met criteria proposed by Daniels and Talal.[7] Data from 14 patients who completed the study were eligible for analysis. Patients expressed no clear preference for treatment with HCQ or placebo with respect to symptoms of dry eye, ocular inflammation, or dry mouth. In addition, patients did not prefer either treatment with regard to fatigue, parotid swelling, myalgia, or arthralgia. A significant reduction in levels of IgM and IgG and a trend toward a decrease in ESR were noted. Lacrimal gland function, as measured by Schirmer's test, rose bengal test, tear lysozyme, and tear lactoferrin concentration, was unchanged. Nine patients studied by technicium and gallium scintigraphy demonstrated no significant change in excretion pattern. An open-label study comparing HCQ (6 mg/kg per day) to IFN-α revealed no effect of HCQ on tear production, salivary flow, or IgG levels.[8] Fox and colleagues[9] conducted a 2-year open-label trial of HCQ in 50 consecutive patients who had primary SS who met San Diego criteria. Forty completers were compared with 10 patients who dropped out of the study for a variety of reasons before completing 6 months. Significant improvements were noted in the majority of indicators related to dry eye, dry mouth, and constitutional symptoms. Ophthalmologic examination revealed significant improvement in rose bengal scores and in blepharitis but not in dryness as assessed by Schirmer's test. In a small, open-label, controlled study, these investigators demonstrated reductions in levels of serum IgG and cross-reactive idiotype-positive RF in patients who had SS and who were receiving 200 mg of HCQ daily.[10] In an open-label study of 14 patients who had primary SS and met European community criteria,[11] Tishler and colleagues[12] found improvement in salivary interleukin (IL)-6 at 6 months and improvement in ESR, C-reactive protein (CRP), and serum IgG at 12 months. Serum IgM and IgA were unchanged. A minority of patients reported improvement in dry mouth, salivary gland swelling and arthralgias. Glandular function was not measured.

Differences among these studies include lack of a formal control group for all except the double-blind trial performed by Kruize and colleagues, use of different criteria for classification, and use of different outcome measures. In addition, study populations were demographically diverse (Netherlands, California, and Israel). HLA–DRB1, DQA1, and DQB1 alleles that confer enhanced risk for primary SS display polymorphisms that are in part associated with geographic distribution.[13] Thus, differences in study populations may have contributed to the differences in reported outcomes. HCQ improves inflammatory biomarkers and likely results in improvement in joint symptoms. Little evidence to date indicates improvement in sicca parameters. A large, multicenter, randomized controlled trial of HCQ is required to demonstrate functional benefits.

ORAL IMMUNOSUPPRESSIVE AGENTS

Methotrexate (MTX) has been used successfully for the treatment of RA for 25 years. Little is known regarding the effect of MTX on secondary SS in patients who have RA. Skopouli and colleagues[14] evaluated the safety and efficacy of MTX for primary SS in a 1-year, open-label pilot trial involving 18 patients; one dropped out after 1 month. All patients met European Community criteria and had a positive minor salivary gland biopsy. Patients received 0.2 mg/kg (10–15 mg) of MTX weekly. Significant improvement in subjective signs of dry mouth and dry eyes was observed, whereas objective improvement as measured by Schirmer's test, rose bengal staining, tear break-up time (BUT), and unstimulated salivary flow (USF) was not seen. Parotid gland enlargement was significantly improved as was dry cough. ESR decreased in three patients at 1 year. Seven (41%) required reductions in MTX dosing secondary to transaminase elevations. MTX seems to deserve further study in a large randomized controlled trial utilizing regimens ranging from 0.2 to 0.4 mg/kg per week.

Azathioprine has been used widely to suppress allograft rejection and to treat a variety of autoimmune disorders, including systemic lupus erythematosis (SLE), RA, and autoimmune hepatitis. The NZB/NZW F1 hybrid mouse, often used as model of systemic lupus erythematosus, also develops lymphocytic infiltrates in the salivary and lacrimal glands similar to that seen in SS. Yeoman and Franklin[15] studied the responsiveness of lymphocytic sialadenitis developing in NZB/NZW mice to treatment with azathioprine early in the course of disease (14 weeks of age) and late in the disease course (26 weeks of age). A dosage equivalent to 2 to 2.5 mg/kg per day in humans was used.

The data showed a trend toward improvement for the azathioprine treated mice for all grades of submandibular and lacrimal gland involvement and for animals treated early and later in the course of disease. Subsequently, Price and colleagues[16] conducted a 6-month randomized, double-blind, placebo-controlled trial of azathioprine (1 mg/kg per day) in 25 patients who satisfied European Community criteria for the classification of SS. Nineteen patients completed 6 months of therapy. All noncompleters were in the azathioprine group. No improvement in tear production by Schirmer's testing, salivary flow, subjective symptoms of dry eye or dry mouth, or laboratory parameters, including serum total IgG and ESR, was noted for the azathioprine group. Rebiopsy of seven patients revealed no pre- or post-treatment differences in focus score or grade. Although evaluated on small numbers of patients, azathioprine does not seem to be a strong candidate for further study for the glandular component of primary SS.

On the basis of previously demonstrated effects on RF and immunoglobulin levels in RA studies, ter Borg and colleagues[17] examined the effect of oral D-PA in a prospective open-label study in 19 patients who had primary SS classified using the European Community criteria. Eight patients dropped out during dose escalation (to 500 mg per

day) leaving 15 patients who underwent treatment with D-PA (250 mg per day) for 3 months and 11 patients who received 500 mg per day for an additional 3 months. A significant increase in USF was observed at 3 months for the treated group. At 6 months, nonstatistically significant improvement was noted in Schirmer's test scores, symptoms of dry eye, ocular foreign body sensation, and dry mouth by visual analog scale (VAS). Significant decreases in ESR and serum IgA and IgM but not IgG were seen. Asahina and colleagues[18] described two patients in whom D-PA (300 mg per day) treatment resulted in improvement in chronic sensory ataxic polyneuropathy associated with SS. One patient had failed previous high-dose oral corticosteroid and oral cyclosporine A (CycA) therapy, the other failed intravenous (IV) pulse methylprednisolone and moderate-dose oral corticosteroid. Because of its high dropout rate and known adverse effect profile, it is unlikely that D-PA will be studied further for SS.

Immunohistochemical studies of exocrine tissue in SS show predominant infiltration with helper T cells. The Th1 subset of these cells is an important source of proinflammatory cytokines, including IFN-γ and IL-2. Antigen binding to T cells activates calcineurin, which in turn dephosphorylates the transcription factor, nuclear factor of activated T cell transcription complex (NFATc). This results in up-regulation of IL-2 transcription. Calcineurin inhibitors are effective inhibitors of T cell IL-2 production and have been used extensively to inhibit rejection of transplanted organs in humans. Thus, calcineurin inhibitors merit study for the treatment of SS. Drosos and colleagues[19] performed a 6-month, double-blind, placebo-controlled trial of CyA (5 mg/kg per day) on 20 patients who had primary SS. Patients had two of three of the following criteria: keratoconjuctivitis sicca, xerostomia by diminished salivary flow, and recurrent salivary gland involvement. In addition, all patients had a positive minor salivary gland biopsy. The mean age of the treatment group was 47 years. Treated patients improved in subjective measures of xerophthalmia, xerostomia, and parotid enlargement; however, this improvement was significant only for xerostomia. Objective measures (Schirmer's test and parotid flow rate) were not significantly improved. Rebiopsy showed that although salivary gland lymphocytic infiltration improved in only two treated patients, it worsened in only one and remained stable in five, whereas in the placebo group salivary gland histopathology worsened in six and was unchanged in two. The most prevalent side effect was hirsutism. A 1-year, open-label, follow-up study[20] included nine patients originally treated with CycA who received the drug for an additional 6 months and nine of the original placebo group who received the drug for 6 months. Results were similar to those described previously for the 6-month, double-blind study except that salivary gland histopathology worsened after 12 months. CycA treatment results in a limited degree of subjective improvement and no significant improvement in objective parameters. Two patients dropped out of the double-blind trial as a consequence of side effects. Of the remaining 18, 18 adverse events were noted at 12 months. In contrast, topical CycA for ophthalmic use results in significant improvement in ocular sicca symptomatology and tear production and is approved for use in dry eye associated with keratoconjunctivitis sicca.

Tacrolimus is a macrolide calcineurin inhibitor that is more potent than CycA. Systemic tacrolimus therapy is used clinically to suppress rejection of organ transplantation. Topical tacrolimus is used for control of atopic dermatitis. Tacrolimus was investigated as a treatment for the Sjögren's-like syndrome that develops in MRL-*lpr*^{cg} mice.[21] Early treatment (2–6 weeks of age) of MRL-*lpr*^{cg} mice with Tacrolimus (2 mg/kg three times per week, intraperitoneally) resulted in significant reductions in lacrimal and submandibular gland mononuclear cell infiltration at 5 months of age, whereas late treatment (from 3 months of age) had no effect. It is anticipated that the newer T cell/IL-2 modulating agents, including tacrolimus, sirolimus, and pimecrolimus, will be studied as disease-modifying agents for SS.

ORAL INTERFERON-α

Although the precise etiology of SS is unknown, it is presumed that an environmental trigger, most likely viral, stimulates the innate immune system, which results in the enhanced elaboration of IFN-α by plasmacytoid dendritic cells and T-cell activation. Despite this, levels of IFN-α have been reported to be depressed in SS. It has been hypothesized that therapy with oral interferon may restore salivary gland function. Shiozawa and colleagues[22] performed a 6-month, single-blinded, controlled trial involving 56 patients who had SS and who received 150 IU of interferon or 250 mg of sucralfate orally. This study demonstrated a significant increase in salivary flow by the Saxon test for the interferon group, although only 50% of the IFN-treated individuals responded. Nine interferon responders underwent rebiopsy of minor salivary glands. Seven of nine showed improvement in the degree of lymphocytic infiltration. Ship and colleagues[23] examined the effect of multiple dosages of oral interferon lozenges in a phase II placebo-controlled trial over a 12-week period in 111 patients fulfilling European Community criteria. Complete responders needed to demonstrate a 25% improvement in the VAS for oral dryness and a 0.05 g per minute increase in unstimulated salivary flow. The percentage of patients achieving complete remission was higher in the groups receiving higher interferon doses (150 u three times a day, 450 u daily) compared with the low-dose (150 u daily) or placebo groups although these differences did not achieve statistical significance. Increases in stimulated salivary flow did reach significance for the 150 IU three-times-a-day group by week 12. Based on these data, a phase III trial examined the efficacy of the 150 IU three-times-a-day dose of interferon in 497 patients who had primary SS.[24] Treated patients had a significant increase in unstimulated whole salivary flow (USF). Increased USF demonstrated a significant positive correlation with improvement in symptom scores for ocular and oral dryness. The primary endpoint of this study (increases in salivary flow and VAS for oral dryness) was not met. To date, oral low-dose interferon has not received approval for the treatment of SS.

ANTIRETROVIRAL AGENTS

Multiple indirect lines of evidence have implicated retroviruses in the pathogenesis of primary SS. These include SS-like disease occurring in individuals infected with HIV-1, detection of antibodies to p24 *gag* proteins associated with reverse transcriptase activity in patients who have SS, and observation of retroviral-like particles in homogenates of SS salivary glands.[25] Therefore, antiretroviral agents also have been studied for the treatment of primary SS. Zidovudine (azidothymidine) was administered to seven patients fulfilling European Community and San Diego criteria in a 3-month, open-label trial (250 mg twice a day).[26] This study was limited to patients who had disease duration of less than 1 year. Subjective complaints of ocular and oral dryness were significantly improved. Schirmer's test scores, tear BUT, and rose bengal scores all significantly improved. Salivary flow was not measured. Fatigue and fibromyalgia tender points improved significantly, whereas serum biomarkers, including ESR and total IgG, were unaltered. Lamivudine was studied in a double-blind, placebo-controlled trial (150 mg twice a day for 3 months) in 18 patients fulfilling American-European Consensus Criteria (AECC).[25] No significant changes were observed for any measure of salivary flow, tear production, ocular surface disease, or subjective symptoms. Serum biomarkers, including ESR, CRP, and total IgG, IgM, and IgA, tended to worsen in the lamivudine group.

INFLAMMATORY LIPIDS

Essential free fatty acids are precursors of eicosanoids. These lipids serve a multiplicity of proinflammatory, anti-inflammatory, and homeostatic functions mediated via

tissue specific exocrine and autocrine mechanisms. Nonsteroidal anti-inflammatory agents inhibit cyclooxygenases (prostaglandin endoperoxide [PGH] synthase 2 or 1), which inhibit formation of prostaglandin E ($PGE_{1/2}$), prostacyclin ($PGI_{1/2}$), and thromboxane $A_{1/2}$. Administration of the nonsteroidal anti-inflammatory drug, piroxicam, a nonselective cyclooxygenase H (PGH) inhibitor, in the double-blind trial also designed to investigate the effect of corticosteroids (discussed previously),[3] did not improve salivary flow rates, salivary gland histopathology, or subjective symptoms of dryness. Dietary essential fatty acid supplementation has been investigated as an alternate approach to altering the composition of pro-inflammatory lipids. In particular, linoleic acid and gamma-linoleic acid (GLA) have been studied because these lipids are precursors of PGH_1. GLA is metabolized to dihomo GLA, an immediate precursor of PGH_1, which in turn is converted to PGE_1. Manthorpe and colleagues[27] studied the effect of evening primrose oil (Efamol) (500 mg three times a day), a compound containing 73% cis-linoleic acid and 9% GLA, on primary SS. For this study, Efamol was supplemented with Efavit—a mixture of vitamin C, pyridoxine, niacin, and $ZnSO_4$, because these molecules are cofactors in the pathway responsible for conversion of GLA to PGE_1. The Efamol study was designed as a brief, 3-week, double-blind, crossover trial involving 36 patients meeting Copenhagen criteria. Ocular outcome measures studied included Schirmer's test, van Bijsterveld score, BUT, and corneal sensitivity. Of these, only Schirmer's test improved significantly. No significant changes were observed in concentrations of tear electrolytes or lysozyme. Oxholm and colleagues[28] performed a 16-week, placebo-controlled, crossover trial using Efamol (3 g) for an 8-week active treatment period. Ocular outcome measures included Schirmer's test, van Bijsterveld score, and tear lysozyme levels. No differences were seen between groups; however, a significant change in the van Bijsterveld score was noted for the Efamol group when pre- and post-treatment values were compared. No significant change in USF was noted. Theander and colleagues[29] performed a 6-month, double-blind, placebo-controlled study of 90 patients who had primary SS. Patients entering the study initially were required to fulfill Copenhagen criteria. Subsequently, they were retrospectively classified into two groups according to fulfillment of AECC. Patients received GLA (800 or 1600 mg daily) versus placebo. GLA therapy did not improve fatigue, the primary outcome measure, at 6 months. The treatment groups also did not experience significant improvement in Schirmer's test, van Bijsterveld score, or unstimulated salivary flow. Although no differences in response rates were noted for the patients who did and did not meet AEC criteria, those meeting AECC, thus having positive SS-A/B antibodies, positive minor salivary gland biopsy, or both, had lower Schirmer values and less diffuse muscle pain than patients fulfilling Copenhagen criteria alone. The investigators concluded that GLA was not effective for the treatment of SS. A more recent double-blind study examined 40 patients fulfilling AECC who received linoleic acid (112 mg) and GLA (15 mg) twice a day versus placebo for 4 weeks.[30] Tear PGE_1 levels were increased in the treatment group as were ocular symptom scores and corneal staining scores reflecting improvement. BUT and tear secretion were not improved significantly. These investigators suggested further study of systemic omega-6 essential fatty acid administration for the management of ocular symptoms of SS.

HORMONAL SUPPLEMENTATION

Primary SS primarily affects women; therefore, a therapeutic role for sex hormone manipulation has been sought. Nandrolone (Deca-Durabolin) (100 mg intramuscularly

biweekly) was studied by Drosos and colleagues[31] in 20 female patients who had primary SS for 6 months.

A double-blind, placebo-controlled design was used. No significant differences were observed between the Deca-Durabolin and placebo groups in tear flow, parotid flow, labial salivary gland biopsy score, and subjective symptoms of dry eye and dry mouth. ESR did decline significantly over 6 months in the treatment group. Most commonly reported adverse effects were hirsutism and hoarseness. Patients who had SLE, RA, and SS have been noted to have low levels of serum dihydroepiandrosterone (DHEA). Pillemer and colleagues[32] performed a 24-week, randomized, double-blind, placebo-controlled trial of oral DHEA (200 mg per day) in 28 women who had SS who met AECC. Oral DHEA treatment did not result in a significant improvement in symptoms of dry mouth or dry eye, Schirmer's test scores, stimulated salivary flow rates, ESR, or IgG levels. These investigators did not recommend DHEA as oral therapy or as dietary supplementation for patients who had primary SS.

BIOLOGIC AGENTS

TNF antagonists have had a dramatic impact on the course and management of several chronic autoimmune diseases, including RA, inflammatory bowel disease, and the spondyloarthropathies. In light of these successes, it was anticipated that TNF antagonists would be of significant value in the management of additional disorders for which similar autoimmune disease mechanisms are well documented, including SS. Early open-label studies suggested that infliximab might be useful for the treatment of constitutional and sicca manifestations of SS. Steinfeld and colleagues[33] performed an open-label, pilot trial of infliximab on 16 patients who had active SS who met AECC and who were not receiving oral DMARDs. All patients received three infusions of infliximab (0, 2, and 6 weeks) (dose of 3 mg/kg) and were studied through week 14. All patients demonstrated improvement in physician and patient global assessment, tender joint counts, and fatigue. USF remained significantly improved at all evaluation points from week 2 until conclusion at week 14. ESR levels were not significantly improved and serum IgG levels increased significantly. Ten patients who continued to have symptoms at the conclusion of the pilot trial were continued in an open-label trial and received additional infusions of infliximab at approximate 12-week intervals.[34] In two patients, the dose was escalated to 5 mg/kg because of incomplete response at 3 mg/kg. Continued significant improvement was noted for the constitutional parameters and for USF at 50 weeks. ESR and serum IgG were unchanged. In contrast, a 22-week, multicenter, randomized, double-blind, placebo-controlled trial of infliximab involving 103 patients[35] did not demonstrate differences in any endpoint, including global assessments of pain, dryness and fatigue, Schirmer's test score, salivary flow, tender joint count, ESR, CRP, or serum IgG, IgM, and IgA. These patients met AECC and received 5 mg/kg of infliximab IV or IV placebo solution at weeks 0, 2, and 6. Sankar and colleagues[36] conducted a 12-week pilot, double-blind, placebo-controlled trial of etanercept (25 mg subcutaneously twice weekly) in 14 patients, 11 of whom had primary SS; three had secondary SS associated with RA. All patients met San Diego criteria.[1] Etanercept treatment did not result in improvement in dry eyes, dry mouth, Schirmer's test scores, stimulated salivary flow, or serum IgG. ESR did decline significantly by a small (18%) but significant amount. The investigators concluded that a small effect was possible but not likely and did not urge further study of TNF antagonists for the treatment of SS.

ISSUES IN CLINICAL TRIALS OF DISEASE-MODIFYING AGENTS FOR SJÖGREN'S SYNDROME

Despite dramatic advances in the treatment of other autoimmune rheumatic diseases, there is no effective disease-modifying therapy for SS. As outlined in this article, many agents used successfully for other rheumatic diseases have been studied for SS without convincing results. Many challenges in trial design and execution are evident from the studies reviewed. Some are generic to rare disorders, such as SS; others may be specific for SS itself.

1. Number. The number of patients enrolled in the majority of the studies reviewed is small. HCQ, the most extensively studied oral DMARD in SS, has been evaluated in fewer than 100 patients in all reported trials.
2. Inclusion criteria. Recently, a consensus has been building regarding use of the AECC for classification of patients entering clinical trials for SS. Until this time, multiple criteria sets were used. The studies reviewed here use eight different criteria sets for inclusion.
3. Outcome measures. Although international collaborative efforts are underway to develop outcome measures for SS clinical trials, at the present time no uniformity exists regarding measures to detect improvement in glandular dysfunction, extraglandular manifestations, and biomarker activity. Most studies use some measure of tear and saliva production, although these are not standardized. For instance, consensus has yet to be developed regarding the use of anesthetized versus unanesthetized Schirmer's tests and stimulated versus unstimulated salivary flow. Even less agreement exists regarding assessment of systemic disease manifestations. Many studies evaluate arthralgia and fatigue but not extraglandular manifestations, such as neuropathy, pulmonary disease, and vasculitis. Recently, investigators and collaborative outcome groups have begun to develop assessment instruments for systemic disease and for glandular function.[37–40] Optimally, the chosen outcome measures will reflect improvement in the glandular and systemic components. The authors analyzed seven studies.[3,4,6,8,10,12,33] in which a functional outcome measure (salivary flow) and a serum biomarker (IgG) were measured (**Fig. 1**). There was a trend toward a significant positive correlation between improvement in salivary flow and reduction in serum IgG.

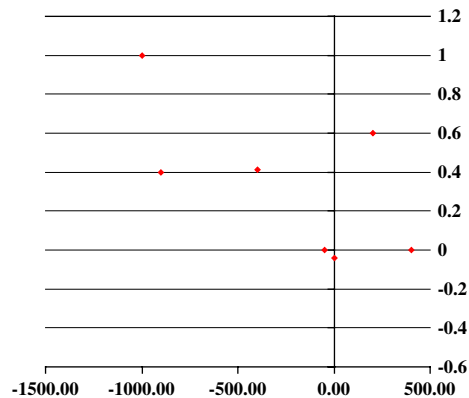

Fig. 1. Correlation between changes in salivary flow rate and changes in levels of total serum IgG in seven studies where a functional outcome measure and a biomarker were recorded. There was a trend toward a significant correlation between decreases in total IgG and increases in salivary flow ($r = 0.58$; $P = .07$).

4. Study design. Significant differences in outcome have been demonstrated among trials performed to evaluate individual DMARDs. **Fig. 2** examines the effect of study design on reported outcomes for glandular function and biomarker activity in studies evaluating HCQ (see **Fig. 2**A) and TNF-α inhibitors (see **Fig. 2**B). Agents that demonstrate efficacy for the treatment of SS in uncontrolled trials generally fail to do so in randomized, blinded, controlled trials. Studies whose outcome measures include sicca manifestations and constitutional symptoms (fatigue or pain) may be particularly prone to environmental, autonomic, and placebo effects. For example, salivary and lacrimal secretion is mediated by autonomic pathways under central nervous system control. Basal lacrimation and salivation are influenced by emotion, such as anxiety and fear. Thus, changes in tear production and salivary flow may be particularly difficult to interpret in uncontrolled studies.
5. Unique biologic properties of lacrimal and salivary epithelium. Agents that have the potential to afford maximal improvement for SS must induce epithelial healing,

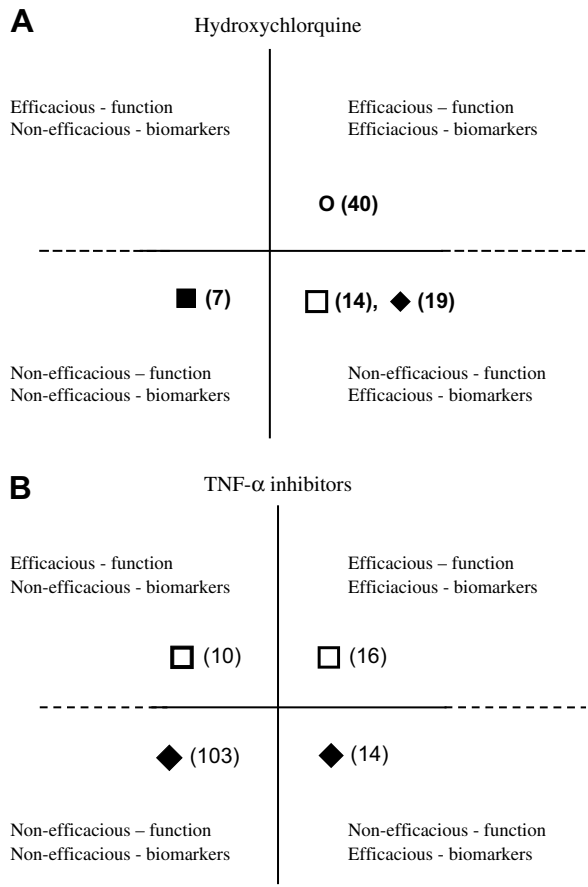

Fig. 2. A 2 $\times$ 2–quadrant display of permutations among possible SS clinical trial functional and biomarker outcomes according to study design. Although retrospective, open-label studies suggest efficacy for HCQ (*A*) and TNF-α (*B*) for SS, prospective, controlled trials do not. Numbers in parentheses correspond to references. ○, retrospective; □, prospective, noncontrolled; ■, prospective, nonblinded, controlled; ◆, randomized, blinded, controlled.

restore function, and inhibit inflammation whereas successful therapies for autoimmune disorders, such as RA may allow for improvement in function solely by blocking the release or action of phlogistic products of inflammatory cells. Therapeutic agents that have clearly demonstrated efficacy in inflammatory diseases (ie, corticosteroids and TNF inhibitors) thus far have failed to exhibit efficacy for SS. In addition, biologic therapeutic approaches that target specific molecules display heterogeneity in clinical efficacy in certain disease states. For instance, inhibition of TNF-α by infliximab results in improvement in Crohn's disease whereas treatment with etanercept does not. Differences in response largely have been attributed to differences in receptor/antibody—ligand-binding affinity or effects on complement activation. Biologic differences in the properties of target tissues require exploration in the design of oral or biologic DMARD therapies for SS. For example, in synovial inflammation where TNF inhibition has been therapeutically successful, TNF-α is expressed in all regions of synovium, particularly in the inflammatory infiltrates and sublining.[41] In SS, where to date TNF-α therapy has been uniformly ineffective, TNF-α is expressed on infiltrating mononuclear cells, ductal epithelial cells but not on acinar end-piece cells.[42]

SUMMARY

To date, published studies and trials of oral and biologic DMARDs for the treatment of SS have shown disappointing results. Improvements in trial design, including development of consortia for the conduct of national and international multicenter studies, use of standardized classification, and outcome measures coupled with the emergence of newer biologic, immunomodulatory, and small molecule agents, hopefully will result in the addition of disease-modifying agents to the armamentarium.

REFERENCES

1. Vivino FB, Al-Hashimi I, Khan Z, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjogren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group. Arch Intern Med 1999;159(2):174–81.
2. Petrone D, Condemi JJ, Fife R, et al. A double-blind, randomized, placebo-controlled study of cevimeline in Sjogren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum 2002;46(3):748–54.
3. Fox PC, Datiles M, Atkinson JC, et al. Prednisone and piroxicam for treatment of primary Sjogren's syndrome. Clin Exp Rheumatol 1993;11(2):149–56.
4. Miyawaki S, Nishiyama S, Matoba K. Efficacy of low-dose prednisolone maintenance for saliva production and serological abnormalities in patients with primary Sjogren's syndrome. Intern Med 1999;38(12):938–43.
5. Miyawaki S, Tojo N. Classification Criteria for Sjogren's Syndrome in Japan. Amsterdam/NY: Kugler Publications; 1994.
6. Kruize AA, Hene RJ, Kallenberg CG, et al. Hydroxychloroquine treatment for primary Sjogren's syndrome: a two year double blind crossover trial. Ann Rheum Dis 1993;52(5):360–4.
7. Daniels TE, Talal N. Diagnosis and differential diagnosis of Sjogren's Syndrome. In: Talal N, Moutsopoulos HM, Kassan SS, editors. Sjogren's syndrome, clinical and immunological aspects. Berlin: Springer Verlag; 1987.
8. Ferraccioli GF, Salaffi F, De Vita S, et al. Interferon alpha-2 (IFN alpha 2) increases lacrimal and salivary function in Sjogren's syndrome patients. Preliminary results

of an open pilot trial versus OH-chloroquine. Clin Exp Rheumatol 1996;14(4): 367–71.
9. Fox RI, Dixon R, Guarrasi V, et al. Treatment of primary Sjogren's syndrome with hydroxychloroquine: a retrospective, open-label study. Lupus 1996;1(Suppl 5): S31–6.
10. Fox RI, Chan E, Benton L, et al. Treatment of primary Sjogren's syndrome with hydroxychloroquine. Am J Med 1988;85(4A):62–7.
11. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjogren's syndrome. Results of a prospective concerted action supported by the European community. Arthritis Rheum 1993;36(3):340–7.
12. Tishler M, Yaron I, Shirazi I, et al. Hydroxychloroquine treatment for primary Sjogren's syndrome: its effect on salivary and serum inflammatory markers. Ann Rheum Dis 1999;58(4):253–6.
13. Carsons S. Sjogren's syndrome. In: Harris ED, Budd RC, Firestein GF, editors. 7th edition, Kelley's textbook of rheumatology, vol II. Philadelphia: Elsevier; 2005. p. 1105–24.
14. Skopouli FN, Jagiello P, Tsifetaki N, et al. Methotrexate in primary Sjogren's syndrome. Clin Exp Rheumatol 1996;14(5):555–8.
15. Yeoman CM, Franklin CD. The treatment of Sjogren's disease in NZB/NZW F1 hybrid mice with azathioprine: a two-stage study. Clin Exp Rheumatol 1994; 12(1):49–53.
16. Price EJ, Rigby SP, Clancy U, et al. A double blind placebo controlled trial of azathioprine in the treatment of primary Sjogren's syndrome. J Rheumatol 1998; 25(5):896–9.
17. ter Borg EJ, Haanen HC, Haas FJ, et al. Treatment of primary Sjogren's syndrome with D-penicillamine: a pilot study. Neth J Med 2002;60(10):402–6.
18. Asahina M, Kuwabara S, Nakajima M, et al. D-penicillamine treatment for chronic sensory ataxic neuropathy associated with Sjogren's syndrome. Neurology 1998; 51(5):1451–3.
19. Drosos AA, Skopouli FN, Costopoulos JS, et al. Cyclosporin A (CyA) in primary Sjogren's syndrome: a double blind study. Ann Rheum Dis 1986;45(9):732–5.
20. Drosos AA, Skopouli FN, Galanopoulou VK, et al. Cyclosporin a therapy in patients with primary Sjogren's syndrome: results at one year. Scand J Rheumatol Suppl 1986;61:246–9.
21. Yang J, Shikata N, Yasuda T, et al. Sjogren's syndrome in mice carrying the Ipr(cg) gene and the therapeutic efficacy of an immunosuppressive agent FK506. Pathol Int 1999;49(2):133–40.
22. Shiozawa S, Tanaka Y, Shiozawa K. Single-blinded controlled trial of low-dose oral IFN-alpha for the treatment of xerostomia in patients with Sjogren's syndrome. J Interferon Cytokine Res 1998;18(4):255–62.
23. Ship JA, Fox PC, Michalek JE, et al. Treatment of primary Sjogren's syndrome with low-dose natural human interferon-alpha administered by the oral mucosal route: a phase II clinical trial. IFN Protocol Study Group. J Interferon Cytokine Res 1999; 19(8):943–51.
24. Cummins MJ, Papas A, Kammer GM, et al. Treatment of primary Sjogren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. Arthritis Rheum 2003;49(4):585–93.
25. Gescuk B, Wu AJ, Whitcher JP, et al. Lamivudine is not effective in primary Sjogren's syndrome. Ann Rheum Dis;64(9)1326–30.
26. Steinfeld SD, Demols P, Van Vooren JP, et al. Zidovudine in primary Sjogren's syndrome. Rheumatology (Oxford);38(9)814–17.

27. Manthorpe R, HagenPetersen S, Prause JU. Primary Sjogren's syndrome treated with Efamol/Efavit. A double-blind cross-over investigation. Rheumatol Int 1984; 4(4):165–7.
28. Oxholm P, Manthorpe R, Prause JU, et al. Patients with primary Sjogren's syndrome treated for two months with evening primrose oil. Scand J Rheumatol 1986;15(2):103–8.
29. Theander E, Horrobin DF, Jacobsson LT, et al. Gammalinolenic acid treatment of fatigue associated with primary Sjogren's syndrome. Scand J Rheumatol 2002; 31(2):72–9.
30. Aragona P, Bucolo C, Spinella R, et al. Systemic omega-6 essential fatty acid treatment and pge1 tear content in Sjogren's syndrome patients. Invest Ophthalmol Vis Sci 2005;46(12):4474–9.
31. Drosos AA, van Vliet-Dascalopoulou E, Andonopoulos AP, et al. Nandrolone decanoate (deca-durabolin) in primary Sjogren's syndrome: a double blind pilot study. Clin Exp Rheumatol 1988;6(1):53–7.
32. Pillemer SR, Brennan MT, Sankar V, et al. Pilot clinical trial of dehydroepiandrosterone (DHEA) versus placebo for Sjogren's syndrome. Arthritis Rheum 2004; 51(4):601–4.
33. Steinfeld SD, Demols P, Salmon I, et al. Infliximab in patients with primary Sjogren's syndrome: a pilot study. Arthritis Rheum 2001;44(10):2371–5.
34. Steinfeld SD, Demols P, Appelboom T. Infliximab in primary Sjogren's syndrome: one-year followup. Arthritis Rheum 2002;46(12):3301–3.
35. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). Arthritis Rheum 2004;50(4):1270–6.
36. Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004;50(7):2240–5.
37. Theander E, Andersson SI, Manthorpe R, et al. Proposed core set of outcome measures in patients with primary Sjogren's syndrome: 5 year follow up. J Rheumatol 2005;32(8):1495–502.
38. Vitali C, Palombi G, Baldini C, et al. Sjogren's Syndrome Disease Damage Index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjogren's syndrome, derived from an analysis of a cohort of Italian patients. Arthritis Rheum 2007;56(7):2223–31.
39. Bowman SJ, Sutcliffe N, Isenberg DA, et al. Sjogren's Systemic Clinical Activity Index (SCAI)–a systemic disease activity measure for use in clinical trials in primary Sjogren's syndrome. Rheumatology (Oxford) 2007;46(12):1845–51.
40. Soloman N, Khlat M, Modi A, et al. Identification of predictive biomarkers in SS clinical trials: a meta-anaylitic approach. J Rheumatol 2005;143–9.
41. Alsalameh S, Winter K, Al-Ward R, et al. Distribution of TNF-alpha, TNF-R55 and TNF-R75 in the rheumatoid synovial membrane: TNF receptors are localized preferentially in the lining layer; TNF-alpha is distributed mainly in the vicinity of TNF receptors in the deeper layers. Scand J Immunol 1999;49(3):278–85.
42. Koski H, Janin A, Humphreys-Beher MG, et al. Tumor necrosis factor-alpha and receptors for it in labial salivary glands in Sjogren's syndrome. Clin Exp Rheumatol 2001;19(2):131–7.

Therapeutic Potential for B-Cell Modulation in Sjögren's Syndrome

Xavier Mariette, MD, PhD

KEYWORDS

• Sjogren's syndrome • B cell • BAFF/BLyS • Rituximab

B-CELL HYPERACTIVITY IN SJÖGREN SYNDROME

B-cell hyperactivity has been recognized for a long time in Sjögren's syndrome (SS). More than 30 years ago, Talal and colleagues[1] demonstrated an increased level in beta2-microglobulin (beta2-m) in the serum of patients with SS, and, more than 20 years ago, Moutsopoulos and colleagues[2] found increased levels of light chains of immunoglobulins in the urine of patients with SS.

Indeed, SS is the autoimmune disease where B-cell activation is the most prominent. This B-cell activation is firstly polyclonal but can progress to monoclonal B-cell lymphoproliferation.[3] A relative risk of 44 for lymphoma was determined by Kassan and colleagues[4] in 1978. A recent study in Sweden and a meta-analysis found a readjusted relative risk of between 16 and 18.[5,6] Nonetheless, SS remains the autoimmune disease where the risk of lymphoma is the most important. It is now clearly evident that lymphoma frequently develops at sites of autoimmunity (salivary glands) and arises from autoreactive B lymphocytes.[7,8] Rheumatoid-factor activity expressed by membrane immunoglobulin could be present in more than 50% of the cases.[9]

Before lymphoma development, B-cell hyperactivity can be evidenced by hypergammaglobulinemia of all isotypes, the presence of autoantibodies, such as anti-SSA and anti-SSB, high level of rheumatoid factor, increase in beta2-m serum levels, and in serum-free light chains of immunoglobulins. Gottenberg and colleagues[10,11] recently demonstrated that serum beta2-m and free immunoglobulin light-chain levels were associated with systemic involvement of the disease.

AN INCREASE IN BAFF COULD EXPLAIN B-CELL HYPERACTIVITY IN SJÖGREN'S SYNDROME

BAFF transgenic mice initially develop a disease-mimicking systemic lupus erythematosus (SLE) followed by a sialadenitis resembling SS, and yet have a twofold increased

Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris-Sud 11, Le Kremlin Bicêtre, Institut Pour la Santé et la Recherche Médicale (INSERM) U 802, France
E-mail address: xavier.mariette@bct.aphp-paris.fr

Rheum Dis Clin N Am 34 (2008) 1025–1033
doi:10.1016/j.rdc.2008.08.014 **rheumatic.theclinics.com**
0889-857X/08/$ – see front matter

risk of lymphoma.[12] Interestingly, data are most compelling to support a role for BAFF in pathogenesis of these three disorders.

Serum BAFF in Sjögren's Syndrome

One year after a role for BAFF had first been identified in human lupus, Groom and colleagues[13] demonstrated that BAFF transgenic mice developed sialadenitis. In this 2002 article, the investigators also demonstrated a higher serum BAFF level in 41 patients with SS.[13] This finding was confirmed in 2003 by demonstrating the correlation between serum BAFF and IgG levels, as well as with rheumatoid factor levels.[14] Moreover, in this study, patients with anti-SSA/SSB antibodies had a higher level of serum BAFF than patients without these autoantibodies. Thereafter, all the studies that assessed serum BAFF level in SS found an increase in this cytokine, and most of them confirmed the correlation with the autoantibody levels.[15–17]

BAFF is Secreted by Resident Cells of Target Organs of Autoimmunity

The first report by from Groom and colleagues showed the presence of BAFF within the salivary lymphoid infiltrate characteristic of this disease. Later, Lavie and colleagues[18] demonstrated that both the T cells of the infiltrate and the epithelial cells could express BAFF. This was confirmed by subsequent studies. Recently, Daridon and colleagues[19] suggested that the B cells of the infiltrate that are the targets of BAFF can also express the ligand and BAFF receptors, leading to an autocrine pathway for BAFF secretion and activation of B cells.[19]

Several groups have demonstrated that salivary epithelial cells may express and secrete BAFF, both in patients with SS and healthy subjects.[19,20] Interestingly, this expression is largely increased by stimulation with type 1 or type 2 interferon (IFN).[20] Patients with SS seem to be more sensitive to the effect of type 1 IFN for the induction of BAFF expression and secretion by salivary epithelial cells.

In recent years, it has been clearly demonstrated than SLE and SS share many common immunopathogenic features, especially an IFN signature which is present in peripheral blood mononuclear cells and targeted organs in both diseases (salivary glands in SS and kidneys in SLE).[21–23] In parallel to IFN-signature expression, BAFF is increased in the target organs of SS: the salivary glands and the conjunctival epithelial cells.[23] Moreover, it has recently been demonstrated that stimulation of salivary epithelial cells by poly(I:C) or by infection of the cells by reovirus, a double stranded RNA virus, induces strong expression and secretion of BAFF.[24] Thus, BAFF could be a possible bridge between innate and adaptive immunity in SS.

Increase of BAFF Could Explain the Lack of Efficacy of Anti-Tumor Necrosis Factor in Sjögren's Syndrome

Two randomized controlled trials, one with infliximab[25] and one with etanercept,[26] demonstrated absence of efficacy of tumor necrosis factor (TNF) blockers in SS. Recent work has showed the reason of the failure of anti-TNF therapy. SS patients experienced an increase in type 1 interferon and BAFF secretion while on etanercept but not placebo, which could explain the absence of improvement.[27]

RITUXIMAB IN SJÖGREN'S SYNDROME

Rituximab, a monoclonal anti-CD20 antibody, has been approved for the treatment of anti-TNF refractory rheumatoid arthritis (RA). Three randomized controlled studies have demonstrated its efficacy in this disorder.

Targeting B cells seems also very promising in SS. To date, rituximab has been used in three open studies, which included 15 to 16 subjects,[28–30] and in case reports of lymphomas complicating SS (**Table 1**).[31–38] In two of these open studies,[28,30] efficacy for dryness was restricted to patients with early diseases. The third open study included patients with systemic complications because B-cell hyperactivity is higher in this category of patients.[29] There was a clear effect of rituximab on systemic complications, including parotidomegaly, synovitis, and cryoglobulinemia-associated vasculitis. Individual cases with lung and renal involvement also improved. In this study, however, there was no change in subjective or objective dryness.

Recently, the first randomized, controlled trial of rituximab in SS was published.[39] Unfortunately, it included only 17 subjects without any systemic complications and studied fatigue as a primary end-point by visual analogic scale (VAS). Because of the low number of patients, there was no statistically significant difference between the two groups in terms of SS-related symptoms; however, the decrease of fatigue was statistically significant only for the rituximab group (decrease of around 50%). This decrease was approximately 20% in the placebo group.

Of note, in these four studies using rituximab in SS, 10% to 20% of treated patients developed serum sickness disease 3 to 7 days after rituximab infusion. This complication must be differentiated from immediate infusion reactions, which are probably because of cytokine release and which usually do not recur after subsequent infusions. Serum sickness may occur after treatment with chimeric antibodies. Curiously, it is exceptional with rituximab treatment of lymphoma and has not been described in the randomized, controlled trials of rituximab in RA. Cases of serum sickness have also been described in open studies of rituximab in lupus. The higher frequency of serum sickness in SS may be because of hypergammaglobulinemia, which is much more common in this disease than in RA. This complication is benign in most cases (fever, arthralgia, and purpura) but forbids further treatment with rituximab.

INCREASE OF BAFF AFTER RITUXIMAB THERAPY

In all autoimmune diseases, treated serum BAFF levels have increased after rituximab therapy. This phenomenon has been shown for RA,[40,41] SLE, and SS.[42,43] This increase has been attributed to the disappearance of BAFF-binding B cells in peripheral blood. This mechanism exists; however, two independent studies[41,42] have shown that, beyond this stoichiometric increase after disappearance of B cells, there was also a true homeostatic feedback characterized by increased BAFF mRNA expression in monocytes after rituximab administration. This increase in BAFF after rituximab could favor the stimulation of new autoimmune B cells. Using BAFF-targeted therapy after rituximab to avoid this increase in BAFF appears to be a promising therapeutic approach.

OTHER B-CELL TARGETED THERAPY

An open study including 15 subjects has been recently performed to evaluate epratuzumab, an anti-CD22 monoclonal antibody[44] for SS. This anti-B-cell antibody leads to only partial B-cell depletion (50% in blood). The results of this open study are interesting, demonstrating improvement in dryness, fatigue, and pain VAS. Moreover, salivary flow seems to be improved in patients with early disease.

Table 1
Efficacy and indications of Rituximab reported in previously published studies

Authors,Years	Number of Patients	Indications of Rituximab	Efficacy for Lymphoma	Efficacy for Systemic Features	Efficacy for Objective Dryness	Efficacy for Subjective Dryness	Adverse Events
Somer, 2003[31]	1	Lymphoma	Yes	NR	Yes	Yes	No
Voulgarelis, 2004[32]	4	Lymphoma (4/4)	4/4 (100%)	3/3 (100%)	NM	NM	2/4 (50%) 2 IRR
Harner, 2004[33]	1	Lymphoma	Yes	NR	NM	Yes	NM
Ramos-Casals, 2004[34]	2	Lymphoma (2/2)	Yes	NR	NM	NM	NM
Pijpe, 2005[35]	1	Lymphoma	Yes	NR	Yes	Yes	No
Gottenberg, 2005[a,50]	6	Lymphoma (2/6) Systemic features (4/6)	1/2 (50%) NR	NR 4/4 (100%)	N (0/2)	3/6 (50%)	2/6 (33%) 1 SSR, 1IRR
Ahmadi-Simab, 2005[36]	1	Scleritis	NR	Yes	NM	NM	NM
Pijpe, 2005[28]	15	Lymphoma (7/15) Early pSS (8/15)	3/7 (43%)	NM	28.6% (2/7) 100% (7/7)	Yes	6/14 (43%) 3 SSR, 2 IRR
Ring, 2005[37]	1	Renal tubular acidosis	NR	No	Yes	Yes	No
Voulgarelis, 2006[38]	6	Lymphoma (6/6)	6/6 (100%)	3/6 (50%)	NM	No	2/6 (33%)
Seror 2007[29]	16	Lymphoma (5/16) Systemic features (11/16)	4/5 (80%) NR	NR 9/11 (82%)	2/16 (18%)	5/16 (36%)	4/16 (25%) 2 SSR, 2 IRR
Devauchelle 2007[30]	16	Pain, dryness and fatigue	NR	1/1 (lung)	No	Yes	2 IRR
Dass 2008[39]	8 (RCT)	Fatigue	NR	NR	No	?	1 SSR, 2 IRR

Abbreviations: IRR, Infusion-related reaction; NM, Not mentioned; NR, Not relevant; RCT, Randomized controlled trial; RTX, Rituximab; SSR, Serum sickness-like reaction.

[a] Four patients are common between the two studies.

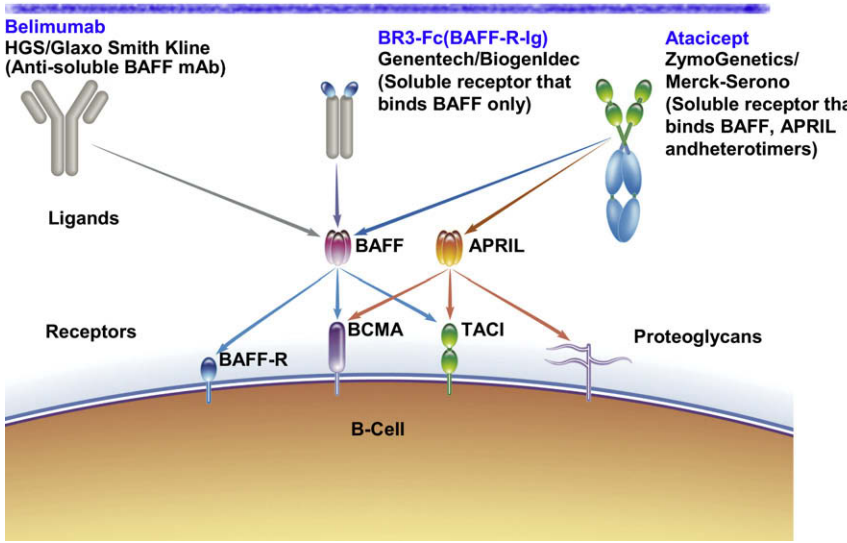

Fig. 1. The three treatments on development inhibiting BAFF or BAFF plus APRIL.

BAFF-TARGETED THERAPY

BAFF is clearly implicated in pathogenesis of SLE and SS. The role of APRIL is less clear, but could be even more important in local stimulation of B-cells within the synovium of RA patients. Thus, neutralizing BAFF or APRIL is tempting in human autoimmunity. To date three different drugs have been designed (**Fig. 1**): Belimumab, a monoclonal anti-BAFF antibody that targets only BAFF; Atacicept, a TACI-Fc molecule that targets both BAFF and APRIL; and BR3-Fc, which targets only BAFF.

To date, two large phase 2 studies (400 to 500 subjects each) have been conducted with belimumab. In RA, the results have been rather disappointing, with an approximate 30% American College of Rheumatology 20 response in all belimumab groups versus 15% in the placebo group.[45] This may be explained by the fact that, as indicated above, B-cell activation in RA may not be driven only by BAFF. In SLE, results have been more encouraging, although the primary end-point (decrease of SLE disease activity index of more than three points) was not achieved in a study involving 449 subjects. A subanalysis restricted to the 70% of subjects with antinuclear antibodies or anti-DNA antibodies showed a significant effect of belimumab in decreasing activity of the disease as measured by SLE disease activity index and anti-DNA antibody level.[46] Phase 3 studies of belimumab are in progress in SLE to confirm these preliminary results, and phase 2 studies in SS should begin soon. Phase 2 studies with atacicept and BR3-FC are in progress in RA.

Recently, data from the first phase 1 study with an antitype 1 IFN monoclonal antibody in SLE was presented, demonstrating good safety and promising efficacy.[47] Obviously, inhibiting type 1 IFN may lead to adverse side effects. In diseases where an IFN signature has been demonstrated, BAFF-targeted therapy could be safer and efficient as an alternative IFN-targeted treatment.

SUMMARY

B-cell modulation is clearly a very promising therapy for SS. Randomized, controlled trials are now needed for the assessment of these new drugs. Two points are critical for designing these new trials.

It is mandatory to have an available activity outcome measure for this disease. After the very interesting preliminary work of Vitali and colleagues[48] and Bowman and colleagues,[49] an international consensus Sjögren's activity score is being developed under the umbrella of the European League Against Rheumatism.

B-cell modulation is probably efficient in SS, but it is certainly not useful for all patients. It is critical to use appropriate inclusion criteria for these future trials to study the correct target population. Initial studies should focus on patients with systemic complications, those with early disease, and those demonstrating increased B-cell biomarkers.

REFERENCES

1. Talal N, Grey HM, Zvaifler N, et al. Elevated salivary and synovial fluid beta2-microglobulin in Sjogren's syndrome and rheumatoid arthritis. Science 1975; 187:1196–8.
2. Moutsopoulos HM, Steinberg AD, Fauci AS, et al. High incidence of free monoclonal lambda light chains in the sera of patients with Sjogren's syndrome. J Immunol 1983;130(6):2663–5.
3. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjogren's syndrome. Arthritis Rheum 2002;46:741–7.
4. Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. Ann Intern Med 1978;89:888–92.
5. Theander E, Henriksson G, Ljungberg O, et al. Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 2006;65:796–803.
6. Zinteras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med 2005;165:2337–44.
7. Royer B, Cazals-Hatem D, Sibilia J, et al. Lymphomas in patients with Sjögren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites and are not associated with viruses. Blood 1997;90:766–75.
8. Voulgarelis M, Dafni UG, Isenberg DA, et al. Malignant lymphoma in primary Sjogren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjogren's Syndrome. Arthritis Rheum 1999;42:1765–72.
9. Bende RJ, Aarts WM, Riedl RG, et al. Among B cell non-Hodgkin's lymphomas, MALT lymphomas express a unique antibody repertoire with frequent rheumatoid factor reactivity. J Exp Med 2005;201:1229–41.
10. Gottenberg JE, Busson M, Cohen-Solal J, et al. Correlation of serum B lymphocyte stimulator and beta2 microglobulin with autoantibody secretion and systemic involvement in primary Sjogren's syndrome. Ann Rheum Dis 2005; 64(7):1050–5.
11. Gottenberg JE, Aucouturier F, Goetz J, et al. Serum immunoglobulin free light chain assessment in rheumatoid arthritis and primary Sjögren's syndrome. Ann Rheum Dis 2007;66(1):23–7.
12. Mackay F, Woodcock SA, Lawton P, et al. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J Exp Med 1999; 190:1697–710.
13. Groom J, Kalled SL, Cutler AH, et al. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjogren's syndrome. J Clin Invest 2002; 109:59–68.

14. Mariette X, Roux S, Zhang J, et al. The level of BLyS (BAFF) correlates with the titre of autoantibodies in human Sjogren's syndrome. Ann Rheum Dis 2003;62: 168–71.
15. Jonsson M, Szodoray P, Jellestad S, et al. Association between circulating levels of the novel TNF family members APRIL and BAFF and lymphoid organization in primary Sjögren's syndrome. J Clin Immunol 2005;25(3):189–201.
16. Pers JO, Daridon C, Devauchelle V, et al. BAFF overexpression is associated with autoantibody production in autoimmune diseases. Ann N Y Acad Sci 2005;1050: 34–9.
17. Pers JO, d'Arbonneau F, Devauchelle-Pensec V, et al. Is periodontal disease mediated by salivary BAFF in Sjögren's syndrome? Arthritis Rheum 2005;52: 2411–4.
18. Lavie F, Miceli-Richard C, Quillard J, et al. Overexpression of BAFF in T cells infiltrating labial salivary glands from patients with Sjögren's Syndrome. J Pathol 2004;202:496–502.
19. Daridon C, Devauchelle V, Hutin P, et al. Aberrant expression of BAFF by B lymphocytes infiltrating the salivary glands of patients with primary Sjögren's syndrome. Arthritis Rheum 2007;56:1134–44.
20. Ittah M, Miceli-Richard C, Gottenberg JE, et al. B-cell activating factor of the TNF family (BAFF) is expressed under stimulation by interferon in salivary gland epithelial cells in primary Sjögren's syndrome. Arthritis Res Ther 2006;8:R51.
21. Bave U, Nordmark G, Lofgren T, et al. Activation of the type-I interferon system in primary SS. Arthritis Rheum 2005;52:1185–95.
22. Hjelmervik TO, Petersen K, Jonassen I, et al. Gene expression profiling of minor salivary glands clearly distinguishes primary Sjogren's syndrome patients from healthy control subjects. Arthritis Rheum 2005;52:1534–44.
23. Gottenberg J, Cagnard N, Lucchesi C, et al. Activation of interferon pathways and plasmacytoid dendritic cell recruitment in target organs of primary Sjögren's syndrome. Proc Natl Acad Sci U S A 2006;103:2770–5.
24. Ittah M, Miceli-Richard C, Gottenberg JE, et al. Viruses induce high expression of B cell-activating factor by salivary gland epithelial cells through toll-like receptor- and type-I interferon-dependent and -independent pathways. Eur J Immunol 2008, 18 March; [Epub ahead of print].
25. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome. Results of the randomized controlled trial of remicade in primary Sjögren's syndrome (TRIPSS). Arthritis Rheum 2004;50:1270–6.
26. Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004;50:2240–5.
27. Mavragani CP, Niewold TB, Moutsopoulos NM, et al. Augmented interferon-alpha pathway activation in patients with Sjögren's syndrome treated with etanercept. Arthritis Rheum 2007;56:3995–4004.
28. Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum 2005; 52:2740–50.
29. Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjogren's syndrome. Ann Rheum Dis 2007;66:351–7.
30. Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum. 2007; 57:310–7.

31. Somer BG, Tsai DE, Downs L, et al. Improvement in Sjogren's syndrome following therapy with rituximab for marginal zone lymphoma. Arthritis Rheum 2003;49(3): 394–8.
32. Voulgarelis M, Giannouli S, Anagnostou D, et al. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. Rheumatology (Oxford) 2004;43(8):1050–3.
33. Harner KC, Jackson LW, Drabick JJ. Normalization of anticardiolipin antibodies following rituximab therapy for marginal zone lymphoma in a patient with Sjogren's syndrome. Rheumatology (Oxford) 2004;43(10):1309–10.
34. Ramos-Casals M, Lopez-Guillermo A, Brito-Zeron P, et al. Treatment of B-cell lymphoma with rituximab in two patients with Sjogren's syndrome associated with hepatitis C virus infection. Lupus 2004;13(12):969–71.
35. Pijpe J, van Imhoff GW, Vissink A, et al. Changes in salivary gland immunohistology and function after rituximab monotherapy in a patient with Sjogren's syndrome and associated MALT lymphoma. Ann Rheum Dis 2005;64(6): 958–60.
36. Ahmadi-Simab K, Lamprecht P, Nolle B, et al. Successful treatment of refractory anterior scleritis in primary Sjogren's syndrome with rituximab. Ann Rheum Dis 2005;64(7):1087–8.
37. Ring T, Kallenbach M, Praetorius J, et al. Successful treatment of a patient with primary Sjogren's syndrome with Rituximab. Clin Rheumatol 2006;25(6):891–4.
38. Voulgarelis M, Giannouli S, Tzioufas AG, et al. Long term remission of Sjogren's syndrome associated aggressive B cell non-Hodgkin's lymphomas following combined B cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Ann Rheum Dis 2006;65(8):1033–7.
39. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjogren's syndrome with rituximab: results of a randomised, double-blind, placebo controlled pilot study. Ann Rheum Dis 2008;67:1541–4.
40. Cambridge G, Stohl W, Leandro MJ, et al. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment: relationships with B cell depletion, circulating antibodies, and clinical relapse. Arthritis Rheum 2006;54:723–32.
41. Toubi E, Kessel A, Slobodin G, et al. Macrophage function changes following rituximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis 2007; 66(6):818–20.
42. Lavie F, Miceli-Richard C, Ittah M, et al. Increase of B-cell activating factor of the TNF family (BAFF) after rituximab: insights into a new regulating system of BAFF production. Ann Rheum Dis 2007;66(5):700–3.
43. Pers JO, Devauchelle V, Daridon C, et al. BAFF-modulated repopulation of B lymphocytes in the blood and salivary glands of rituximab-treated patients with Sjögren's syndrome. Arthritis Rheum 2007;56:1464–77.
44. Steinfeld SD, Tant L, Burmester GR, et al. Epratuzumab (humanised anti-CD22 antibody) in primary Sjögren's syndrome: an open-label phase I/II study. Arthritis Res Ther 2006;8(4):R129.
45. Stohl W, Chatham W, Weisman M, et al. Belimumab (BmAb), a novel fully human monoclonal antibody to B-lymphocyte stimulator (BLyS), selectively modulates B-cell sub-populations and immunoglobulins in a heterogeneous rheumatoid arthritis subject population. Arthritis Rheum 2005;52:S444.
46. Petri M, Furie R, Ginzler E, et al. Novel combined response endpoint and systemic lupus erythematosus (SLE) flare index (SFI) demonstrate belimumab (Fully

human monoclonal antibody to BLyS) improves or stabilizes SLE disease activity and reduces flare rate over 2.5 years of therapy. Arthritis Rheum 2007;56:S527.
47. Wallace DJ, Petri M, Olsen N, et al. MEDI-545, an anti-interferon alpha monoclonal antibody, shows evidence of clinical activity in systemic lupus erythematosus. Arthritis Rheum 2007;56:S526.
48. Vitali C, Palombi G, Baldini C, et al. Sjögren's Syndrome Disease Damage Index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjögren's syndrome, derived from an analysis of a cohort of Italian patients. Arthritis Rheum 2007;56(7):2223–31.
49. Bowman SJ, Sutcliffe N, Isenberg DA, et al. Sjögren's Systemic Clinical Activity Index (SCAI)—a systemic disease activity measure for use in clinical trials in primary Sjögren's syndrome. Rheumatology (Oxford) 2007;46(12):1845–51.
50. Gottenberg JE, Guillevin L, Lambotte O, et al. Tolerance and short-term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005;65:913–20.