

## **Update on Sjögren's Syndrome From ACR 2008**

### **Introduction**

Advances in the diagnostic methods of, the pathogenesis of, and therapy for Sjögren's syndrome (SS) were presented at the American College of Rheumatology (ACR) 2008 Annual Scientific Meeting. This report summarizes the clinical features and pathogenesis of SS as well as new treatment advances.

### **Overview of Clinical, Therapeutic, and Pathologic Features**

Background information in regard to SS and the general rheumatologist was reviewed during the ACR Clinical Review Course, Medical Update Sessions, and in the Sjögren's Study Group Sessions. Key advances in SS were reviewed.

Clinically, SS is manifested by:

- Keratoconjunctivitis sicca;

- Xerostomia; and

- Characteristic autoantibodies, including antinuclear antibody (ANA) and anti-Sjögren's syndrome A (SS-A) antibody or a minor salivary gland biopsy with a focus score of 1 or greater.

Criteria for the assessment of disease activity and extent of organ damage are currently in development.

Although the SS-A and SS-B antibodies are part of the diagnostic criteria, it should be recognized that some patients with SS may lack these antibodies, and conversely healthy individuals without SS may possess these antibodies. Other patients with SS have anticentromere antibodies (ACA) but still clinically behave like patients with primary SS. The presence or absence of particular antibodies should serve as a guide to diagnosis of SS, but neither confirms nor excludes the diagnosis.

Other important antibodies reported in patients with SS include antimuscarinic M3 receptor and antifodrin antibodies. These latter 2 antibodies may play a role in pathogenesis, but methodologically, in the clinical setting, they have been difficult to detect in a reproducible manner

with immunofluorescent or enzyme-linked immunosorbent assay (ELISA) methods.<sup>[1,2]</sup>

Pathologically, biopsies of the lacrimal and salivary glands show:

Focal infiltrations of lymphocytes that have been further characterized by their cell-surface markers and cytokine/growth factor production profiles.

Changes in the vascular endothelial cells and dendritic cells that produce characteristic molecules that govern lymphocyte homing, retention in the gland, and survival/apoptotic factors.

Alteration in glandular (acinar and ductal) elements, including aquaporins and other molecules that serve as transporters of ions, defensins, and cytokines/growth factors. The saliva and tears of patients with SS exhibit quantitative and qualitative differences in their content of proteins from normal.

Disorganization of the extracellular matrix of the glands due, in part, to characteristic metalloproteinases.

One of the most prevalent myths about SS is that dryness results from the total destruction of the lacrimal and salivary glands by the immune system. However, only about 50% of the glandular elements are "destroyed" in patients with severe dryness. The remaining ducts/acini do not function because of the inflammatory process that disrupts the ability of the residual secretory units to either release or respond to neurotransmitters, such as acetylcholine and vasoactive intestinal peptide.

Treatment for SS includes:

Topical therapy, ie, "artificial tears"; however, this form of therapy vary in terms of preservative (a preserved tear should not be used more than 4 times/day), viscosity (several different vehicles), and osmolality;

Punctual occlusion and medicated tears, including topical cyclosporine, and limited use of corticosteroid-containing drops can be helpful;

Recognition of blepharitis and the maintenance of the tear film layer (see below);

Topical treatment of dry mouth with artificial salivas and other lubricants; Oral agents, such as pilocarpine and cevimeline;

Systemic therapy that includes hydroxychloroquine and agents similar to the treatment of systemic lupus erythematosus (SLE); and

Investigative use of biologic agents (discussed below).

Patient evaluation and education can be particularly challenging in patients with SS because symptoms include general fatigue and vague cognitive

dysfunction, as well as depressive and demyelinating disorders. These symptoms can be a significant cause of "disability" from the patient's perspective, and sometimes can be confused with fibromyalgia. The patient's complaint of dry eye is exacerbated by the increased evaporative loss associated with inflammation of the meibomian glands, a condition known as "blepharitis."<sup>[3-7]</sup>

The rate of evaporative loss depends on:

*The lipid layer,*  
*The outside ambient humidity; and*  
*The blink rate.*

Each of these factors may be important in treating the patient with dry or painful eyes.

## **Criteria for Disease Activity and Disease Damage Indices**

The study group that spearheaded the new consensus criteria have recently presented an activity and disease damage index<sup>[8]</sup> that will serve as a starting point for uniform clinical data collection and research studies. These indices will provide the same type of standardization that the ACR criteria provided for rheumatoid arthritis (RA). However, the task is more complex than the RA criteria, and the problems of generating measures for evaluating SS are more comparable to that of SLE. Indeed, the new criteria for SS later are based on similar measures in SLE, such as the Safety of Estrogens in Systemic Lupus National Assessment (SELENA) and British Isles Lupus Assessment Group (BILAG), in which the absence of definitive biomarkers has made disease assessment difficult. It should also be noted that the new measures extend the work of Bowman and coworkers<sup>[9]</sup> in the development of a clinical disease activity index that was acknowledged as a basis for the Vitali scores.<sup>[8]</sup>

## **The Role of Mucins in SS**

It has long been recognized that there is no close relationship between lacrimal gland flow rates, as measured by Schirmer's test, and a patient's symptoms of ocular dryness.<sup>[3,10]</sup> Tears do have an aqueous component, but also have *proteins* and *mucins* that form a lubricating protective gel.<sup>[4]</sup> The tears have a different composition in terms of mucins, osmolality, and proteins compared with saliva. Also, the lipid component of the tears (secreted by the meibomian glands, discussed below) is important in slowing down evaporation.<sup>[3,5,11-16]</sup>

Thus, the volume of tears is determined by its aqueous content produced by the lacrimal gland, as well as the mucins<sup>[6]</sup> ( especially MUC4) produced by goblet cells of the ocular surface that contribute to the viscosity of the tear film.<sup>[3-6]</sup> The number of goblet cells can be ascertained by simple exfoliative cytology of the conjunctival surface or by conjunctival biopsy,<sup>[17]</sup> a method generally used in research or in clinical trial settings.

Similarly, there is a poor correlation between measurement of saliva and patient's complaints of dry mouth.<sup>[18-20]</sup> This may reflect the misconception that saliva is "water" rather than a complicated mixture of water, proteins, and mucins. This lubricating film provides a reduced viscosity for the oral mucosa and allows the tongue to more easily function during deglutition and talking.<sup>[21]</sup>

In a recent report,<sup>[22]</sup> reduced sulfating of mucin MUC5B was more closely linked to complaints of xerostomia in patients with SS than aqueous water flow. Mucins are sulfated oligosaccharides that sequester water to provide lubrication and low viscosity of movement of the oral mucosa. They are familiar to many of us as the Lewis antigens that are secreted in saliva. This defect in sulfating of MUC5B probably results from the inflammatory microenvironment due to release of cytokines and the disorganization of the basal lamina as a result of metalloproteinases that lead to dedifferentiation of the acinar mucous cells.<sup>[22]</sup>

## **Highlighted Specific Presentations**

Meijer and coworkers<sup>[23]</sup> reported results of their double-blind, placebo-controlled study on rituximab treatment in patients with primary SS.

This study reported a statistically increased stimulated whole-saliva secretion; saliva flow increased from 0.77 mL/minute to 0.87 mL/minute at 12 weeks after 2 infusions of 1 g each (time, 0 and 2 weeks). Both the control and rituximab groups received methylprednisolone 100 mg at time 0 and then tapered over the next 2 weeks. Although the standard deviations of the flow rates were quite high, the difference did reach statistical difference. Due to differences in methodology, it is difficult to compare this study with previous studies. Of note, the National Institute of Health-sponsored, multicenter rituximab trial also failed to show a statistically significant difference in salivary flow.<sup>[24]</sup>

Perhaps, the inclusion of patients relatively early in their disease who exhibited residual saliva production may have contributed to the failure to show a statistical improvement in saliva flow with treatment. However, in

the Meijer study,<sup>[23]</sup> the patients did show improvement of oral and ocular symptoms on a Visual Analogue Scale, although the objective evaluation of tear flow did not reach statistical significance. Overall, the observed changes with treatment remain relatively small and with large standard deviations; treated patients reverted to their baseline dryness by 6 months.

Nonetheless, this study is important because clinical trials for licensing rituximab with the US Food and Drug Administration (FDA) will require improvement in the patients' most characteristic symptoms (ie, keratoconjunctivitis sicca), and the patients included in the study (those earlier in the disease course and with residual saliva flow) represent the subgroup of patients with SS who should be studied.

Vivino and coworkers<sup>[25]</sup> demonstrated the utility of salivary scintigraphy to monitor treatment of SS. Six patients enrolled in a rituximab trial were studied with dynamic sequential imaging. In patients who had residual salivary gland activity at the start of the study, 3 of 4 patients showed demonstrable improvement at 6 months after therapy. Tools, such as scintigraphy, are relatively noninvasive and will be a key component of drug therapy trials for FDA drug registration.

Bikker and coworkers<sup>[26]</sup> presented the result of their study on the correlation between expression of interleukin (IL)-7 and immunopathology in the exocrine glands of patients with SS. They examined minor salivary gland biopsies from 30 patients with SS using immunohistology and studied the saliva/sera levels of IL-7 by the enzyme-linked immunosorbent assay (ELISA) method. Their study demonstrated a consistent increase in IL-7 expression in the vicinity of focal lymphocytic infiltrates. Furthermore, cytokine was produced by the endothelial cells, a minority of CD68 macrophages, and by cells with fibroblast morphology.

This study presents new information and perhaps a new therapeutic target. IL-7 cytokine and the hepatocyte growth factor form a heterodimer that functions as a pre-pro-B-cell growth-stimulating factor. In addition, this cytokine is a cofactor for V(D)J rearrangement of the T-cell receptor beta during T-cell development. Mice knockout studies suggested that this cytokine plays an essential role in lymphoid cell survival.

In a separate study, Bikker and colleagues<sup>[27]</sup> demonstrated that IL-7 stimulation is not suppressed by T-reg cells found in the SS salivary gland; this finding strengthens the argument that IL-7 may be an important therapeutic target. Previously, this cytokine has been shown to be produced locally by intestinal epithelial and epithelial goblet cells, and may

serve as a regulatory factor for intestinal mucosal lymphocytes. It is a suggested target for therapy of Crohn's disease<sup>[24]</sup> and anti-IL-7 antibodies (as well as toxin-conjugated IL-7R antibodies) -- currently in clinical trials.<sup>[28,29]</sup>

Ittah and coworkers<sup>[30]</sup> presented the results of their study investigating whether the retinoic acid-inducible gene I (*Rig-1*) and melanoma differentiation-associated gene 5 (*MDA5*) are involved in BAFF expression by reovirus 1-infected salivary epithelial cells. Their study demonstrated high induction of BAFF by salivary gland epithelial cells after viral infection. This study also sheds some new light on the mechanisms of induction of autoimmunity by innate immunity. This study also expands previous studies on the role of endosomal Toll-like 3 receptor<sup>[31-33]</sup> by demonstrating a mechanism that is independent of endosomal processing and stimulates high levels of BAFF.

*Rig-1* is an RNA helicase that has an essential function in the innate immune response to double-stranded RNA viruses. As suggested in the studies by Ittah and colleagues<sup>[30]</sup> and Bave and coworkers,<sup>[31,33]</sup> cellular apoptotic debris might mimic the "antiviral response" and thus serve to initiate or perpetuate the local immune response.

Ambulatory cardiovascular monitoring is used to determine the relative balance of the adrenergic and cholinergic systems. This method has been used in performance athletes for some years with the devices described in the report. It may provide useful objective information in regard to patients' symptoms of fatigue and other complaints related to posture.

Although statistically significant differences were not demonstrated in the entire group, it is important to bring this simple method to the attention of rheumatologists, as we now send patients to cardiologists for expensive tilt-table tests. It is surprising that autonomic dysfunction was not noted in this study, as previous studies in patients with RA and SLE have noted significant differences from controls.<sup>[34,35]</sup>

Sekiguchi and colleagues<sup>[36]</sup> reported the results of their study on the ratio of T17 and Forkhead box P3 (FoxP3) T cells (T-regs) in salivary gland biopsies. Their ratio is affected by sphingosine-1-phosphate (S1P), and their presentation extended the abstract by showing that S1P inhibitors, such as fingolimod (FTY720), may help bias the lymphocytic infiltrates in favor of T-regulatory cells. S1P may be an important target because studies have demonstrated a therapeutic benefit of oral fingolimod in treatment of multiple sclerosis and in murine models of SS.<sup>[37,38]</sup>

The study by Nordmark and coworkers<sup>[39]</sup> demonstrated that a relatively small proportion of patients with SS (15%) have at least 4-fold higher susceptibility alleles and an impressively increased odds ratio of developing SS. This study expands a recent publication of an association of interferon regulatory factor (IRF)5 haplotypes in SLE.<sup>[40]</sup>

In patients with SLE, type 1 interferons clearly contribute to disease activity and damage. IRF5 genetic variation has been found to be strongly associated with SLE susceptibility in studies performed in white and Asian populations. However, the underlying genetic structure of this association is complex. The associations include both a correlation with disease susceptibility and a correlation with protective components, and at least 3 polymorphisms are known to be involved. According to one point of view, these 3 polymorphisms jointly modulate the susceptibility to SLE on 3 different levels: susceptible, neutral, and protective.

The relationship of these polymorphisms in IRF5 and signal transducer and activator of transcription (STAT)4 may provide further information on the complicated patterns of interaction.

Clinical features of SS were also highlighted in a number of very interesting poster presentations. Soto and coworkers<sup>[41]</sup> provided updates of the chronic and insidious evolution of pulmonary involvement in a cohort of 61 patients with SS. Specifically, the prevalence of pulmonary involvement was 12%, with bronchiectasis being the most frequent finding. By the 10-year follow-up, 24% of patients had significant pulmonary findings; interstitial lung disease appeared early in the course of SS.

Massara and coworkers<sup>[42]</sup> presented a retrospective study of central nervous system involvement in a cohort of patients with SS. They used a panel of expert neurologists to determine "true" neuropsychiatric manifestations -- including vasculitis, brain demyelinating disorders, transverse myelitis, stroke, and seizure -- in contrast to vague fibromyalgia symptoms. They found true neuropsychiatric manifestations as a rare (5.7%) but not negligible subset. This data are reassuring to rheumatologists who are frequently presented with multiple neurologic complaints as part of the fibromyalgia-like features that accompany SS.

Bonazza and coworkers<sup>[43]</sup> noted early small-fiber involvement in patients with SS, even before the onset of clinical symptoms. They used quantitative sensory tests to determine sensory thresholds to warmth and cooling with respect to cutaneous blood flow, measured by laser Doppler of the foot compared with the proximal thigh and skin biopsy performed at

the proximal thigh and distal leg. These methods have been used in patients with diabetes<sup>[44]</sup> for over a decade, and the current study expands a recent publication by Chai and colleagues.<sup>[45]</sup>

Segal and coworkers<sup>[46]</sup> reported the relationship between patients' cognitive functioning and cognitive performance. They found that depression and cognitive impairment are overlapping but independent aspects of patients' clinical picture. Executive function and verbal memory measures are associated with subjective cognitive dysfunction, and these abnormalities in the cognitive domains are consistent with the hypothesis that frontal subcortical patterns of brain involvement may be affected in SS.

Meiners and coworkers<sup>[47]</sup> reported on the impact of SS on quality of life, employment, and disability in 1000 Dutch patients. They found a significant impact on employment and disability, as reflected by lower Short Form (SF)-36 Health Survey scores, lower employment rates, and higher disability rates compared with the general Dutch populations. Fibromyalgia symptoms and vague cognitive dysfunction were adverse predictors of outcome.

## **Summary**

The 2008 ACR meeting presented an excellent balance of clinical reviews and recent advances on the pathophysiology and treatment of SS, as well as updates on the ophthalmologic and oral features of SS. These updates are very relevant to rheumatologists who treat patients with SS because they are increasingly seeing themselves at the hub of the medical system as the "coordinator of care" for problems ranging from ophthalmology, oral medicine, neurology, and other medical or surgical issues.

Clinical studies in large European cohorts revealed the adverse effects of SS on quality of life and disability. Advances in therapy appeared to focus on studies on rituximab, in which it appears that patients with residual function may show improvement in slow rates and patient/physician-rated improvement for up to 6 months.

However, new targets for therapy -- including IL-7, other cytokines, and S1P -- may prove promising in the future.

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