Clinician’s Corner

Systemic Activity at Diagnosis of Sjögren’s: A Key Prognostic Marker

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Laboratory of Autoimmune Diseases "Josep Font", CELLEX, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Department of Autoimmune Diseases, ICMiD, Hospital Clinic, Barcelona, Spain

Introduction

Sjögren’s is a systemic autoimmune disease in which immune-mediated inflammation causes secretory gland dysfunction, leading to dryness of mucosal surfaces and systemic organ involvement. The disease may occur at all ages but is often diagnosed in the fourth to sixth decades of life with a female: male ratio of 10:1.¹ The variability in disease presentation may partially explain delays in diagnosis of up to 10 years from the onset of symptoms.* On the one hand, Sjögren’s is a disease that can be expressed in many guises depending on the specific epidemiological, clinical, or immunological features. Sjögren’s also may be a serious disease with an excess of mortality mainly related to systemic involvement and B-cell lymphoma.² The autoimmune origin is often confirmed by positivity of circulating autoantibodies, and some laboratory abnormalities may support the clinical suspicion of Sjögren’s, including normocytic anemia, mild leukopenia and, especially, high serum gammaglobulin levels and a severely-raised erythrocyte sedimentation rate.

*The SSF Breakthrough Goal “To shorten the time to diagnose Sjögren’s by 50% in five years!” is making tremendous progress in the time to diagnosis.

Updates from the 13th International Symposium on Sjögren’s

Introduction by Roland Jonsson DMD, PhD, 13th ISSS Conference Chair
Professor, The Broegelmann Chair in Immunology, The Gade Institute, University of Bergen, Bergen, Norway

Introduction

The 13th International Symposium on Sjögren’s Syndrome (ISSS), Bergen, Norway, May 19-22, 2015 was conducted by Roland Jonsson and his team, with an attendance of approximately 260 participants from five continents. The full 2015 ISSS program is available at: http://sicca.org/issss2015, where photos from the event also can be viewed. The nearly 200 abstracts from the meeting were published in the May issue of the Scandinavian Journal of Immunology 2015(81):329-450.
Onset of the disease: more than sicca features

Although Sjögren’s is often considered a chronic, non-life threatening disease overwhelmingly dominated by dryness, fatigue and pain, systemic involvement is increasingly recognized as part of the disease spectrum, since it is present at diagnosis in 70–80% of patients and plays a key role in prognosis, with the joints, lungs, skin and peripheral nerves being the organs most frequently involved. Three multicenter studies including more than 2,500 European patients recently confirmed that Sjögren’s is, undeniably, a systemic autoimmune disease with severe systemic manifestations being reported in 15% of patients, especially those with an immunological profile suggestive of B cell activation.

Systemic features may be the presenting manifestation or appear after the disease is diagnosed and clearly mark disease prognosis. Although severe, life-threatening systemic involvement is unusual in Sjögren’s, it may account for nearly 10% of deaths. Cryoglobulinemic vasculitis is the life-threatening condition most frequently reported in Sjögren’s patients, with the involvement of vital organs such as the kidneys, lungs and gastrointestinal tract. Other severe involvement has been reported, including central nervous system features, progressive ataxic neuropathy, pulmonary arterial hypertension and severe thrombocytopenia or autoimmune hemolytic anemia.

Scoring systemic activity in Sjögren’s

The development of the EULAR Sjögren’s Disease Activity Index (ESSDAI) by the EULAR Task Force Group on Sjögren’s represents a step forward in the evaluation of systemic disease. The EULAR promoted an international collaboration between more than 40 experts to develop two consensus disease activity indexes in Sjögren’s, the EULAR Sjögren’s Syndrome Patients Reported Index (ESSPRI, a patient-administered questionnaire to assess subjective symptoms) and the ESSDAI. The ESSDAI includes specific organ-by-organ definitions and allows homogeneous evaluation of systemic features in large series of patients.

The identification, at diagnosis, of markers prospectively associated with a poor prognosis could play a significant role in identifying patients requiring a closer follow-up. In a recent study published in the Annals of Rheumatic Diseases, we evaluated the potential link between baseline systemic activity using the ESSDAI and mortality in a large cohort of patients with Sjögren’s.

Understanding mortality in Sjögren’s

Mortality in Sjögren’s has been mainly attributed to systemic disease and lymphoma. Involvement of two internal organs that have the greatest influence on the survival of patients with Sjögren’s are the lungs and the kidneys. Sjögren’s-related pulmonary disease is clearly associated with decreased quality of life and survival, with a 2- to 4-fold increase in the risk of death compared with patients without pulmonary disease. With respect to renal involvement, a recent study including 35 Greek patients...
with biopsy-proven renal involvement found high rates of adverse outcomes, including chronic renal failure (31%), lymphoma (26%) and death (26%), especially in patients with cryoglobulinemic-glomerulonephritis.

As with other autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis, mortality in Sjögren’s is not only related to the autoimmune disease itself. In our recent study, 115 out of 1,045 patients (11%) died after a mean follow-up period of 117.4 months (range 6-388 months), of which 101 were female and 14 male, with a mean age at death of 76.4 years. The survival curve of the entire cohort showed that the survival at 5, 10, 20 and 30 years after the diagnosis was 96.0%, 90.5%, 80.9% and 60.4%, respectively. The main causes of death were cardiovascular disease in 35 patients, infections in 21, systemic disease in 18, haematological neoplasia in 10 and other causes in 21; in the remaining 10 cases, the cause of death was unknown or unclassifiable (See Figure 1). In addition to systemic disease and lymphoma, we identified two additional prominent causes of death: infection (an unexpected finding that deserves specific analysis in a further study) and cardiovascular disease, which has recently been associated with Sjögren’s. Therefore, our patients with Sjögren’s had an excess of mortality due to multiple causes, although the predominant etiologies were unrelated to Sjögren’s itself (infections and cardiovascular disease). A possible explanation for the lesser role of autoimmune complications might be the lower frequency of end-stage organ failure caused directly by Sjögren’s, together with the excellent prognosis of the most frequent type of haematological neoplasia reported in our patients (low-grade MALT lymphoma).

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most severe extraglandular manifestations of Sjögren’s are often related to cryoglobulinemic disease; cryoglobulins are closely associated with other immunological prognostic markers (hypocomplementemia, monoclonal band); and patients with cryoglobulinemia are at a higher risk of developing B-cell lymphoma. Patients with cryoglobulinemia at diagnosis of Sjögren’s, especially when there is vasculitic involvement, should be closely followed and treated early due to the high risk of adverse outcomes.

In our recent study, we found that the main baseline factors associated with overall mortality in the multivariate analysis were male gender, cryoglobulins and low C4 levels. Baseline activity in the constitutional, pulmonary and biological domains was associated with a higher risk of death. High activity in at least one ESSDAI domain, a baseline ESSDAI score ≥14 and more than one laboratory predictive marker (lymphopenia, anti-La, monoclonal gammopathy, low C3, low C4 and/or cryoglobulins) were associated with overall mortality; these HRs increased 3 to 10-fold when the analysis was restricted to mortality associated with systemic disease. Table 1 summarizes the main factors associated with a worse prognosis (development of lymphoma and/or low survival) in patients with Sjögren’s.

Table 1: Main factors associated with worse prognosis (development of lymphoma and/or low survival) in patients with Sjögren’s

<table>
<thead>
<tr>
<th>a) Clinical features</th>
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<tr>
<td>• Parotid enlargement</td>
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<td>• Purpura</td>
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<td>• High systemic activity (ESSDAI)</td>
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<th>b) Diagnostic tests</th>
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<tr>
<td>• Severe scintigraphic involvement (grade IV)</td>
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<th>c) Laboratory abnormalities</th>
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<tr>
<td>• Leukopenia</td>
<td></td>
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<tr>
<td>• CD4+ lymphopenia</td>
<td></td>
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<tr>
<td>• CD4/CD8 ratio &lt; 0.8</td>
<td></td>
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<tr>
<td>• Beta2 microglobulin levels</td>
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<tr>
<th>d) Immunological parameters</th>
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<tr>
<td>• Cryoglobulins</td>
<td></td>
</tr>
<tr>
<td>• Hypocomplementemia</td>
<td></td>
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<tr>
<td>• Monoclonal band</td>
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<tr>
<td>• Anti-La/SSB</td>
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<td>• BAFF levels</td>
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**Practical recommendations for follow-up**

The diagnostic approach in patients with suspected Sjögren’s is complex and requires a complete and systematic workup focused not only on glandular involvement but also on the systemic components of the disease. The clinical approach to Sjögren’s patients presenting with systemic involvement requires diagnostic tests that not only adequately confirm systemic involvement but also rule out other etiologies not directly related to Sjögren’s. In systemic patients, other systemic autoimmune diseases and non-autoimmune processes that may frequently be diagnosed in patients aged > 50 years (cardiovascular disease, diabetes mellitus, neurodegenerative diseases and cancer) must be ruled out. A very careful workup in differentiating systemic Sjögren’s from other systemic and autoimmune diseases is mandatory for some specific...
systemic presentations that are found very infrequently in Sjögren’s without another accompanying major rheumatic disease: erosive arthritis, infrequent location of arthritis, extracutaneous non-cryoglobulinemic vasculitis, pericarditis and pleurisy, pancreatitis or proximal renal tubular acidosis, among others. In these patients, specific autoantibodies related to other systemic autoimmune diseases should be provided for the majority of systemic involvement (negativity will confirm “primary” Sjögren’s in these patients).

Although we found that the total mean ESSDAI score at diagnosis did not correlate with survival, a specific analysis of the subset of patients presenting with a very high level of activity at diagnosis showed a significant association. Patients with the highest level of activity at diagnosis in at least one domain had a higher mortality rate, as did those who had a high baseline score (ESSDAI ≥14) according to the categories proposed by the EULAR Sjögren’s Task Force Group. A practical message is that patients with this “high risk” pattern should receive a closer follow-up and, probably, earlier and more robust therapeutic management. These patients may have a high baseline ESSDAI score even in the absence of significant sicca manifestations.

Measurement of systemic activity by the ESSDAI at the time of a Sjögren’s diagnosis should be mandatory, because it is helpful in identifying a specific subset of patients who require closer follow-up. Patients with a clinical presentation principally limited to the mucosal surfaces (mainly dryness, fatigue and pain) without systemic involvement and/or laboratory prognostic markers (baseline ESSDAI score <5) may require only annual evaluation. In contrast, patients presenting with high systemic activity (ESSDAI ≥14) and/or with predictive immunological markers (especially those with more than one) may be closely followed every 3-6 months by a rheumatologist or other specialist in autoimmune disease. Routine physical examination should include examination for peripheral lymphadenopathy and enlargement of parotid glands, the liver and the spleen. Yearly laboratory tests should include full blood count, erythrosedimentation rate, renal and liver function tests. Immunological tests are not necessary in routine follow-up except for markers associated with a poor prognosis (complement levels, cryoglobulins, monoclonal gammopathy), and in patients with a clinical suspicion of development of a concomitant systemic autoimmune disease.

**Sjögren’s: more than a sicca disease**

Until now, the clinical approach of patients with Sjögren’s has been traditionally focused on the study and characterization of glandular involvement, even though Sjögren’s is undeniably more than a sicca disease. In fact, Sjögren’s is still diagnosed using criteria exclusively focused on glandular involvement, and this happens despite the long list of systemic features reported, involving the majority of organs and systems. The need for a consensus on a homogeneous diagnostic and therapeutic approach to systemic involvement in Sjögren’s is clear. The EULAR Sjögren’s Task Force Group is now working on the development of the EULAR Sjögren’s Recommendations for the characterization and treatment of organ-specific extraglandular involvement in Sjögren’s on the basis of a systematic review of the current scientific evidence. A greater understanding of the etiopathogenesis of systemic immune-mediated damage, active international collaborations and the development of international consensus and guidelines is necessary.

In conclusion, it should be remembered that Sjögren’s may initially present with systemic features (See Table 2) and not always with sicca symptoms, and that patients presenting with a high level of systemic activity at diagnosis are at higher risk of developing lymphoma and have a poor prognosis. We need to change the current traditional diagnostic paradigm of waiting for the development of sicca features in order to diagnose Sjögren’s and follow a comprehensive multidisciplinary approach centered on detecting early biological and histopathological signatures of the disease, which may appear several years before the development of a clear, overt sicca syndrome.

### Table 2: Non-sicca manifestations suggestive of Sjögren’s

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Analytic features</th>
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<tbody>
<tr>
<td>Chronic fatigue</td>
<td>Elevated erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>Hypergammaglobulinemia</td>
</tr>
<tr>
<td>Leukocytoclastic vasculitis</td>
<td>Leukopenia and thrombocytopenia</td>
</tr>
<tr>
<td>Recurrent parotid gland swelling</td>
<td>Serum and/or urine monoclonal band</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>Positive antinuclear antibodies or rheumatoid factor</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>in an asymptomatic patient</td>
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<tr>
<td>Neuromyelitis optica</td>
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<tr>
<td>Renal tubular acidosis</td>
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<tr>
<td>Annular erythema</td>
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<tr>
<td>Interstitial lung disease</td>
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<td>Mother of a baby born with congenital heart block</td>
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REFERENCES

“New Diagnostic Tools” opened with an update on current projects using ultrasonography (US) of the major salivary glands, an imaging technique that is emerging as a promising diagnostic tool to detect salivary gland abnormalities in Sjögren’s. A simplified scoring system focusing on the presence of hypoechoic appears feasible for becoming a part of clinical practice and, as such, will optimize the overall evaluation of Sjögren’s patients. For a more objective evaluation of major salivary gland US, an automated digital analysis of major salivary gland ultrasound images was suggested.

Sonoelastography is a relatively new modality in the imaging of salivary glands. Elasticity scores were higher for Sjögren’s and related to disease duration over 10 years. Modern ultrasonographic techniques, such as virtual touch tissue imaging, real time tissue elastography and virtual touch tissue quantification were compared to B-mode ultrasound. Results suggest that virtual touch tissue quantification enables an objective measurement of the glandular stiffness. Another imaging modality, scialoscintigraphy, showed significantly lower up-take of tracer in Sjögren’s patients and less up-take in the submandibular glands compared to the parotid glands, suggesting that scialoscintigraphy could be useful for the functional evaluation of major salivary glands.

A parotid biopsy technique was demonstrated in an informative instruction video summarizing the advantages of the parotid gland biopsies that include, for instance, the possible comparison of parotid gland saliva production with US images in relation to histopathological parameters of the same parotid gland (the saliva-ultrasound-biopsy axis). Systematic literature reviews focused on the fact that different criteria and techniques are used for US evaluation. creating a high

New Diagnostics Tools
by Malin V. Jonsson, DMD, PhD
Associate Professor at Department of Clinical Dentistry – Section for Oral and Maxillofacial Radiology, University of Bergen, Bergen, Norway

The session, “New Diagnostic Tools,” at the 13th International Symposium on Sjögren’s included five oral presentations and seven posters. This session was chaired by Drs. Deborah Greenspan and Malin V. Jonsson.
risk of bias with regard to patient selection and conduction and interpretation of ultrasonography. Further studies are needed for validation and standardization of US techniques and image analysis.

Regarding the diagnosis of dry eye, it was reported that punctual occlusion and topical cyclosporine use can affect the ocular surface staining scores (OSS) and Schirmer’s test and thus influence the diagnosis of Sjögren’s. Patients with punctual occlusion and a low OSS were more likely to have a normal Schirmer’s test than those with a low OSS and no occlusion. A prospective interventional study is needed to determine whether punctual plugs and cyclosporine have an effect on OSS and whether dry eye patients undergoing punctual occlusion increase their tear volume and “normalize” their OSS.

Early detection of Sjögren’s in the future might be achieved by a technique using single-cell autoantibody nanowells (SCAN) to directly identify single B cells producing known antibody markers such as anti-SSA/Ro52, anti-SSA/Ro60, anti-SSB/La, and anti-muscarinic receptor type-III (M3R), analyzing cells from peripheral blood or minor salivary glands.

The detection and diagnosis of autoimmune diseases may be delayed by several years due to subclinical serological and functional abnormalities. This occurrence was illustrated by a likely model of transition from incomplete Sjögren’s to Sjögren’s and identifying a small group of patients not yet fulfilling Sjögren’s criteria but likely to develop Sjögren’s, SLE or overlap syndromes. As for children, the natural course of Sjögren’s is uncertain. Patients with 10 years follow-up of pediatric Sjögren’s were studied, revealing that less than 20% of patients had developed other rheumatic diseases such as juvenile systemic lupus erythematosus or mixed connective tissue disease. When Sjögren’s is diagnosed in pediatric patients, one should consider the possibility for development of other rheumatic diseases; this area warrants further studies.

Patients with sicca symptoms but not fulfilling the diagnostic criteria for Sjögren’s were investigated for IgG4 related disease (IgG4-RD), a disease reported to possibly overlap with Sjögren’s. However, in the absence of a clear clinical suspicion of IgG4-RD, routine IgG4 staining of the labial minor salivary gland biopsy is not of clinical use.

In conclusion, a number of interesting and promising studies have focused on a variety of aspects to obtain, improve and secure the diagnosis of Sjögren’s.

Dr. Robert I. Fox, MD, PhD provided key highlights of the International Symposium on Sjögren’s in a piece for Medscape entitled “Advances in Understanding, Diagnosing, and Treating Sjögren’s.” The full article can be found at http://www.medscape.com/viewarticle/848782. Dr. Fox delineated the many successes of the symposium, including reports on agreement reached on classification criteria for diagnosis of Sjögren’s for clinical trials; guidelines for evaluating efficacy of therapy; and the development of new biomarkers and pathogenic tools. Dr. Fox points out that while dry eyes, dry mouth, and fatigue are often described as “benign” features of Sjögren’s, patients cite these symptoms as a cause of tremendous disability. Fatigue and cognitive dysfunction mark the areas of greatest need for a new therapeutic, and Dr. Fox urges rheumatologists to collaborate with neuroscientists and learn from studies in multiple sclerosis.

**Novel Biomarkers at the ISSS**

by Kathy L. Sivils, PhD; Director, Sjögren’s Research Clinic; and Member, Arthritis & Clinical Immunology Research Program; Oklahoma Medical Research Foundation and, Adjunct Associate Professor, Department of Pathology University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

The etiology and pathogenesis of Sjögren’s is clearly complex and involves multiple mechanisms of disease. This leads to heterogeneity in clinical presentation, prognosis, progression and therapeutic outcomes. Robust biomarkers with clinical utility for each of these purposes are lacking. To date, stratifying patients is largely based on clinical features and does not reflect the underlying molecular mechanisms that contribute to various disease features. This poses a significant barrier for fully realizing the potential benefit of “precision medicine,” by which patients are accurately diagnosed and clinical care is tailored to the cause(s) of disease.

Recent studies aimed at identifying novel biomarkers in Sjögren’s have suggested numerous novel candidates for validation and further study, many of which were discussed at the recent ISSS meeting in Bergen. Various sample types such as saliva and blood have been used with hopes of developing molecular testing that can easily be applied in clinical settings. Many of these candidates

Continued on page 8.
have been discovered using powerful, unbiased, high-throughput technologies to screen for hundreds or even thousands of biomarkers that differentiate patients from healthy controls or define specific patient subsets.

These approaches include genome-wide screens for genetic variants that are enriched in patients and transcriptional profiling of RNA to identify genes and non-coding RNAs with altered expression patterns. Genetic studies have established associations with DNA variants that increase risk of developing Sjögren’s. The genes that are thought to be most affected by these DNA variants play a role in antigen presentation (HLA), Type I interferon pathways (IRF5, OAS1), Type II interferon pathways (STAT4, IL12A), B cell signaling (BLK), lymphocyte trafficking (CXCR5) and NFkb signaling (TNIP1).

RNA transcriptional profiling has identified numerous candidate biomarkers and provided new insights into disease mechanisms. These studies generally compare the levels of various RNA transcripts, including both coding and non-coding RNAs, between patients and controls to assess altered gene activity. Signatures of disease involving hundreds of differentially expressed transcripts have been described and, interestingly, include transcripts that reflect changes in the oral microbiome (Tandon S3.14, Gallo S3.13).

Proteomics approaches using saliva as a substrate have identified not only profiles that correlate with salivary gland dysfunction but also important phenotypic subsets such as presence of exotropic germinal centers (Delaleu, S3.3, Baldini S3.5).

Two exciting new areas for biomarker discovery involve assessment of the microbiome, where the balance between pathogenic and beneficial bacteria may provide useful information, and metabolomics. DNA sequencing approaches have shown differences in the microbial composition of oral, ocular and gut microbiomes in Sjögren’s patients (Siddiqui S3.16, DePaiva S3.17). A
SSF Research Grantee and Fellowship Updates

SSF Research Grantee News: Spotlight on Michael J. Passineau, PhD

Michael J. Passineau’s latest research article, “IL-17 sequestration via salivary gland gene therapy in a mouse model of Sjögren’s syndrome suppresses disease-associated expression of the putative autoantigen Klk1b22” was published in the Arthritis Research & Therapy online journal on August 6, 2015. Some key findings from his manuscript include: 1) the most notable proteomic signatures of IL-17 sequestration on SS-like disease-related proteins were Kallikrein-related peptidases, including the putative autoantigen Klk1b22 and 2) IL-17 sequestration also notably led to an isoelectric shift, but not a molecular weight shift, of Kallikrein-1, attributed to phosphorylation. Dr. Passineau’s research infers that Non-viral IL-17 sequestration gene therapy in the salivary gland is feasible and downregulates expression of a putative SS autoantigen in the Aec1/Aec2 mouse.

Dr. Passineau is the Director for the Gene Therapy Program, Allegheny Health Network and is Associate Professor, Drexel University College of Medicine, at the Allegheny-Singer Research Institute, West Penn Allegheny Health System, in Pittsburgh, Pennsylvania. He was awarded a two-year SSF Innovative Concept Research Grant in 2011 and 2012 for his project entitled “Ultra-sound-assisted gene transfer of IL17R:Fc to the salivary glands as a gene therapy for Sjögren’s Syndrome.”

Reference


SSF Student Fellowship Research Updates:

Kerry Leehan: Minor Salivary Gland Fibrosis in Sjögren’s is a Fundamental Aspect of Pathology

by Kerry Leehan, PhD-Candidate; University of Oklahoma Health Sciences Center and Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma

Editor’s Note: Kerry Leehan was the recipient of the SSF-AADR Student Fellowship in 2013-2014 for her project entitled “Markers and genetic mechanism of fibrosis in Primary Sjögren’s syndrome.”

Historically, fibrosis in the salivary gland has been widely observed but ascribed to age rather than considered a part of the pathology of Sjögren’s. With support from the Sjögren’s Syndrome Foundation-American Association of Dental Research Fellowship award, my research has indicated that fibrosis is a fundamental pathological feature of Sjögren’s and has explored potential serum biomarkers associated with fibrosis.

In Sjögren’s patients meeting AECG criteria (n=68) and sicca-symptom controls not fulfilling criteria (n=60), we conducted a precise quantification of fibrotic replacement in minor salivary gland biopsy tissue. Fibrosis was significantly elevated in patients (median average percent area fibrosis of 26.8%) compared to controls (median of 16.7%; p<0.0001), whereas age was not significantly different between groups (p=0.13). The extent of fibrotic tissue correlated with biopsy focus score (Spearman r= 0.45, p<0.0001), van Bijsterveld score (Spearman r= 0.25, p=0.005), reduced whole unstimulated saliva flow (Spearman r= -0.19, p=0.03)

Continued on page 10 ▼
and a reduction in the total number of teeth present (r=-0.29, p = 0.009). All parameters were measured at the time of lip biopsy.

The SSF-AADR Fellowship specifically funded a pilot study of potential biomarkers of fibrosis. Following a literature review of systemic fibrotic disease, we selected a panel of seven analytes, including RANTES, MIP1α, IL4, IL10, IL-21, galectin, and IL-33 to test using a multiplex ELISA platform (pSS = 48, DNMC = 24). We found a significant elevation of RANTES/CCL5 (p=0.008) in Sjögren’s patients, though no correlation with fibrosis was evident. Interestingly, serum levels of RANTES and focus score were significantly correlated (Spearman r = 0.35, p=0.02) as were fibrosis and focus score in this subset (r=0.39, p=0.001). Although we did not find an association between fibrosis and our tested biomarker candidates, the small size of this pilot study was underpowered for the detection of subtle peripheral differences. We plan to expand these studies, as biomarkers for disease-associated histopathology would offer a non-invasive and potentially beneficial tool in the arsenal of Sjögren’s treatment and patient care.

My graduate research centers on fundamental and immunological features of Sjögren’s pathology. Specifically, I study the contribution of T cells to the glandular environment and the role of fibrosis in disease. I am privileged to be conducting my research with Dr. A. Darise Farris at the Oklahoma Sjögren’s Syndrome Center of Research Translation (OSSCORT) at the Oklahoma Medical Research Foundation in Oklahoma City, Oklahoma. The OSSCORT is comprised of a multidisciplinary team of investigators focused on identifying novel biomarkers, uncovering fundamental immunological mechanisms of disease, and improving patient care under the banner of bench-to-bedside research.

**Scott Walter: Targeted Lipidomic Analysis of Tear Film Eicosanoids in Dry Eye**

*by Scott D. Walter, MD; Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida*

**Editor’s Note:** Scott D. Walter, MD was the recipient of the SSF-CLAO Student Fellowship in 2013-2014 for his project entitled “Targeted Lipidomic Analysis of Tear Film Endocannabinoids.”

Dry eye is a chronic inflammatory disorder of the ocular surface. Previous work in animal models and clinical dry eye studies has implicated arachidonic acid (AA), an omega-6 (Ω-6) fatty acid which is an important precursor to many pro-inflammatory metabolites known as “eicosanoids” in the pathogenesis of dry eye. Omega-3 (Ω-3) fatty acid supplementation is now emerging as an effective treatment paradigm for the management of dry eye. Ω-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are believed to alter the eicosanoid profile in ways that promote resolution of inflammatory lipid circuits on the ocular surface. However, tear film levels of the Ω-3 eicosanoids DHA and EPA have never been measured. In a project supported by a Sjögren’s Syndrome Foundation-Contact Lens Association of Ophthalmologists (CLAO) Student Fellowship award, Scott Walter, MD, with Karsten Gronert, PhD, Anat Galor, MD, and colleagues, conducted a targeted lipidomic analysis of tear film eicosanoids on 41 patients with well-characterized signs and symptoms of dry eye.

The investigation concluded that Ω-3 and Ω-6 fatty acids are present in the dry eye tear lipidome, suggesting activation of both pro- and anti-inflammatory eicosanoid circuits on the ocular surface. Use of systemic NSAIDs and Ω-3 supplements affected the quantity of both Ω-3 and Ω-6 fatty acid precursors in the tear film. Ω-3 supplements were associated with a more anti-inflammatory tear film eicosanoid profile (lower Ω-6:Ω-3 ratio), whereas a more pro-inflammatory eicosanoid profile (higher Ω-6:Ω-3) was associated with black race, arthritis, and tear film dysfunction (decreased TBUT, low Schirmer score, more corneal staining). The AA metabolites prostaglandin E2 (PGE2) and hepoxilin were detected in the majority of dry eye subjects, implicating these specific eicosanoid mediators in the pathogenesis of dry eye. Low PGE2 was associated with NSAID use and tear hyperosmolarity, while high PGE2 was associated with dysfunctional meibum and increased corneal staining. This is the first study to directly measure DHA, EPA, and hepoxilin levels in the human tear film and to correlate pro- and anti-inflammatory eicosanoid profiles with ocular surface disease severity in dry eye. Ongoing work by Dr. Walter and colleagues seeks to characterize the fatty acid ethanolamide-derived eicosanoids (also known as endocannabinoids) in the tear film.

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Industry News

Dry Eye Disease Market Expected to More-Than Double by 2024

According to GlobalData and as reported by Drug Discovery & Development (www.dddmag.com), the Dry Eye Disease (DED) market is expected to increase dramatically. In addition to Allergan’s and Mimetogen’s MIM-D3 that is entering Phase 3 trials and is mentioned below, Shire’s Lifitegrast will provide a novel and potentially blockbuster drug for DED that reduces inflammation and is expected to launch in late 2016. Allergan’s Restasis is expected to expand to European markets next year, and Mitotech’s Visomitin and RegeneRx’s RGN-259 will offer additional first-in-class treatments for DED. Each drug offers different therapeutic pathways and benefits and will move the DED market to US$4.6 billion across nine major international markets (US, France, Germany, Italy, Spain, UK, Japan, China and India), according to GlobalData. Opportunities have increased with improved understanding of DED and the discovery of new therapeutic targets.

Allergan Recalls Several OTC Products for Dry Eye

Please be aware that Allergan is issuing a recall on the following consumer products that are primarily used to treat ocular dryness:

- Refresh Lacri-Lube for dry eye (3.5g and 7g)
- Refresh PM for dry eye (3.5g)
- FML 0.1% -topical anti-inflammatory agent for ophthalmic use (3.5g)
- Blephamide - 10% / 0.2% sterile topical ophthalmic ointment combining an antibacterial and a corticosteroid (3.5g)

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA’s MedWatch Safety Information and Adverse Event Reporting Program either online at www.fda.gov/MedWatch/report, or by calling 800-332-1088.

Allergan-Mimetogen Collaborate on Dry Eye Disease Therapy

Allergan has announced an agreement with Mimetogen Pharmaceuticals to develop and market a new treatment for dry eye disease. Tavilermide (MIM-D3) enhances the ocular tear film by increasing production of mucin and also reduces inflammation. The protein naturally occurs in the eye and maintains corneal nerves and epithelium. The partnership will enable Phase 3 trials using MIM-D3 in dry eye patients to move forward. Phase 2 trials showed significant improvement in signs and symptoms of dry eye.

Janus Biotherapeutics Partners with Roche

Janus Biotherapeutics is collaborating with Roche on the development of a small molecule that targets toll-like receptors (TLRs) in several autoimmune diseases. Research is in the pre-clinical stage. TLRs, proteins involved in the innate immune system, have been shown to be involved in the development of autoimmune disease. Janus is focused on new therapeutics for Sjögren’s as well as SLE, RA, psoriasis and scleroderma.
metabolomics study was presented that showed increased levels of lactate, glutamine, acetate, and threonine and decreased levels of others in the peripheral blood of SS patients compared to healthy controls (Gottenberg S3.6).

Although these exciting new discoveries provide numerous candidate biomarkers, significant challenges remain to identify, validate and qualify those biomarkers that accurately allow stratification of patients for clinical follow-up using therapeutic approaches that are tailored to the precise underlying disease mechanisms. These topics will be the focus of an upcoming conference, “Biomarkers and Targeted Therapeutics in Sjögren’s” (BATTs), to be held in Oklahoma City, Oklahoma on September 19-22, 2017. For more information, please visit omrf.org/batts.

**SSF Presentations**

The Sjögren’s Syndrome Foundation (SSF) had the opportunity to participate in several ISSS presentations. A new session focusing on activities directed by patient advocacy organizations was included for the first time in the ISSS program and was chaired by Stefano Bombardieri, MD (Pisa, Italy) and Steven Carsons, MD (Mineola, New York, USA). The SSF presented its Clinical Practice Guidelines, with Frederick Vivino, MD providing an overview and covering methodology; Steven Carsons, MD speaking on rheumatology recommendations (biologics for sicca and for systemic disease, fatigue, and DMARDs for inflammatory musculoskeletal pain); Michael Brennan, DDS, MHS on oral recommendations (caries prevention); and Stephen Pflugfelder, MD on ocular recommendations.

Following the guidelines presentation, Steven Taylor, SSF CEO, moderated a panel with representatives from the International Sjögren’s Network (ISN) that included France, Norway, and the USA. Groups described some of their major initiatives. Taylor reported on the ISN patient organization survey, which included information gathered from 14 international groups on topics such as patient and physician education, research and drug development, and quality of life for Sjögren’s patients. Abstracts on all four topics were accepted by the ISSS and displayed during the poster session (S6.1, S6.2, S6.3 and S6.4).
The Optometry and Vision Science journal dedicated its entire September 2015 issue to Dry Eye Disease. The issue contains 23 articles, written by leaders in the fields of optometry, physiological optics, and vision science. The following are the articles included in this issue:

- Effects of Isotretinoin on Meibomian Glands
- Altered Mucin and Glycoprotein Expression in Dry Eye Disease
- Ophthalmic Procedures for Treatment of Advanced Ocular Surface Diseases
- Omegas and Dry Eye
- Evidence-Based Management of Dry Eye Disease
- Risk Factors for Dry Eye Syndrome
- Meibomian Gland Atrophy in Daily Contact Lens Wearers
- Binocular Vision Disorders and Contact Lens Discomfort?
- Ocular Surface Disease in Glaucoma: Effect of Polypharmacy & Preservatives
- Glaucoma Medication Use and Dry Eye
- Corneal Neuralgia after LASIK
- Blink Anomaly Contributions to Post-Lasik-Neurotrophic Epitheliopathy
- Ocular Surface Cooling and Tear Film
- Automated and Traditional Measures of Tear Film Breakup
- Tear Film Stability, Osmolarity, and Dryness Symptoms
- Freezing Point Depression Technique Osmometer
- Climate on Clinical Diagnostic Dry Eye Tests
- Corneal Confocal Microscopy in Dry Eye Treated with Corticosteroids
- Topical Cyclosporine and Diquafosol Treatment in Dry Eye
- Intraocular Scattering after Instillation of Diquafosol
- Software to Improve Blinking and Dry Eye Symptoms
- Lid Debridement-Scaling in Sjögren’s Syndrome Dry Eye
- Self-Applied Heat Therapy for Meibomian Gland Dysfunction

The journal is published by the American Academy of Optometry (AAOPT). For more information on this special issue, see http://journals.lww.com/optvissci/Fulltext/2015/09000/OVS_Announces.1.aspx. For more information on AAOPT, visit www.aaopt.org.

Keep a watch for DEWS II!

The SSF traveled to New York for the international Dry Eye Workshop (DEWS) II meeting of the Public Awareness & Education Subcommittee (PAES) in October. SSF Chair-Elect Stephen Cohen, OD and SSF VP of Medical & Scientific Affairs Kathy Hammitt, MA, PAES Chair, participated along with esteemed representatives from the international dry eye community.

DEWS II members are currently hard at work on updating our knowledge about all aspects of Dry Eye Disease, including Definition, Epidemiology, Pathophysiology, The Role of Sex, Gender and Hormones, Iatrogenic DED, Diagnosis, Management and Therapy, and Clinical Trials. DEWS II is organized by TFOS and David Sullivan, PhD and Chaired by J. Daniel Nelson, MD with Vice Chair, Jennifer Craig. The DEWS II report is expected in 2017.
BCG Therapy and Sjögren’s?

Former SSF Medical and Scientific Advisory Chair Denise Faustman, MD, PhD presided over a conference on autoimmune disease therapy in October entitled “Second BCG and TNF Signaling in the Treatment and Prevention of Autoimmune Diseases.” Discussions focused on Bacillus Calmette-Guerin or BCG therapy, a vaccine that has been in use for nearly a hundred years. SSF Vice President of Medical and Scientific Affairs Kathy Hammitt represented the SSF at the meeting and spoke on Sjögren's.

Originally found to be efficacious in preventing tuberculosis (TB), BCG is a generic drug that is a top treatment for some bladder cancers. BCG now has entered Phase 2 clinical trials for Type I Diabetes after earlier positive trials, and recent clinical trials in multiple sclerosis patients appear promising. Dr. Faustman is hoping to launch trials in Sjögren’s in 2016 with Co-PI Ilias Alevizos, DMD, Acting Director and Assistant Clinical Investigator for the NIH Sjögren’s Clinic. BCG is prepared from mycobacterium bovis and induces regulatory T Cells or Tregs.

Dr. Faustman is the Director of the Immunobiology Laboratory at the Massachusetts General Hospital and an Associate Professor of Medicine at Harvard Medical School. She edited a 2014 book entitled “The Value of BCG and TNF in Autoimmunity” and published by Elsevier. For more information on Dr. Faustman’s research in BCG, visit http://faustmanlab.org.

References

Sjögren’s Information Available in Spanish

The National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS), National Institutes of Health (NIH), has introduced a new Spanish-language website that provides free information and resources on health conditions of the bones, joints, muscles and skin. The website also has a page dedicated to information on Sjögren’s which includes a downloadable booklet in Spanish. The launch of the site coincided with National Hispanic Heritage Month this fall.

NIAMS Director Stephen I. Katz said “We are committed to providing quality health information to all people, no matter what language they speak or what culture they identify with.”

Raising awareness and increasing education for patients and families about Sjögren’s is a vital part of the SSF mission. The Foundation is pleased to share that this important information is now available in Spanish: http://www.niams.nih.gov/Portal_en_espanol/Informacion_de_salud/Sindrome_de_Sjogren/default.asp

Sjögren’s Collaboration in China

A major collaboration on the study pathogenesis and treatment of Sjögren’s at Hong Kong University and Tsinghua University School of Medicine in China. A HK$3 million grant was provided from the Croucher Foundation for the initiative over a three-year period starting in January 2016. Professor Chen Dong is leading the collaboration for Tsinghua and Professor Liwei Lu for HKU. For more information, visit: http://www.croucher.org.hk/tsinghua-hku-collaboration-on-sjogrens-syndrome#.Vc3vhnheefQ
Neurological disease is not uncommon in Sjögren’s (SjS) and is often under-recognized. Nerve pain (neuropathic) occurs in ~20% of patients. More than 10% may have Small Fiber Neuropathy (SFN) that is not detected by EMG/NC studies but can be detected by a skin biopsy. SjS patients can have neurological involvement without dry mouth but have the SSA autoantibody or positive lip biopsy at presentation. Furthermore, patients may test negative for SSA/SSB Ab.

- Cognitive Impairment (particularly Executive Function) and Fatigue are very common and debilitating. Treating co-morbidities (depression and/or pain disorders) may help.

- Consider a consultation with a neurologist to define the type of neuropathy: Peripheral (weakness, numbness, and/or pain in peripheral nerves, such as the hands, feet, arms and legs), Autonomic (affecting involuntary bodily functions such as digestion, bladder function, and sweat glands), and Central (brain/spinal cord). A neurologist can exclude conditions such as thyroid and vitamin B deficiencies.

- Take a “Lifestyle Inventory” that includes stress, sleep and nutrition. Any areas for improvement?

- For severe peripheral neuropathies, SNRIs (serotonin-norepinephrine reuptake inhibitors (Duloxetine Cymbalta®, Venlafaxine Effexor®) or neuroleptics/anticonvulsants (Gabapentin Neurontin®) can be tried. TCAs (tricyclic anti-depressants) are often too drying.

- For debilitating peripheral neuropathy, IVIG (intravenous immune globulin) has shown benefit.

- For the rare vasculitic type of neuropathy seen with cryoglobulins or transverse myelitis, steroid, immunosuppressive, Rituximab (Rituxan®) drugs are indicated.

- For gastroenterology (GI) symptoms (constipation, bloating, even intestinal “burning”), consider that small nerve fibers (without myelin) could play a role. Many GI specialists are aware of this, and centers that specialize in GI Motility disorders (NeuroGastroenterology) are available.
The Sjögren’s Syndrome Foundation (SSF) was instrumental in the development of a Continuing Medical Education course on dry eye and Sjögren’s that is now available. The initiative was led by Gary Foulks, MD, University of Louisville, Department of Ophthalmology and Visual Sciences, Louisville, Kentucky. Dr. Foulks is a former Chair of the SSF Board of Directors and current member of the SSF Medical and Scientific Advisory Board. Additional authors are listed below.

The course is designed to improve diagnosis and, ultimately, outcomes for Sjögren’s patients by raising awareness on the part of ocular professionals that their dry eye patients could have Sjögren’s and need to be identified. Coverage includes sections on Dry Eye Disease Taxonomy; Sjögren’s Disease: The Disease State; Diagnosis (including an Algorithm for Diagnosis); Management of Sjögren’s; and information on the SSF as a major resource for healthcare professionals and patients.

Improving Diagnosis and Outcomes of Sjögren’s Disease Through Targeting Dry Eye Patients was jointly sponsored by Candeo Clinical/Science Communications, LLC and the University of Florida College of Medicine. The publication was administered by an independent editorial board and supported by an unrestricted educational grant from Bausch and Lomb/Nicox Inc.

A complimentary link is available through the SSF until December 30, 2015 at http://authors.elsevier.com/a/1S0NH5UdE~F48l. Following that date, the CME can be accessed by subscribers to the The Ocular Surface or with a one-time access fee by non-subscribers.

Reference