

Update on Sjogren's Syndrome: The View from 14th International Sjogren's Syndrome 2018

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I. Introduction

The 14th International Sjogren's Syndrome (SS) symposium (IHSS) was held in Washington, DC from April 18-21, 2018. This interdisciplinary meeting included experts in Ophthalmology, Oral Medicine, Rheumatology and other Internal Medicine specialties, Neurology, Radiology, Pathology and Basic Researchers to discuss diagnostic and clinical advances during the past 3 years.

Members of the FDA (Federal Drug Administration) and pharmaceutical industry presented the guidelines and pathways forward to drug approval. Also, SS patients and their patient organization (Sjogren's Syndrome Foundation (SSF) were present to express their concerns about the impact of SS on their quality of life, and serve as a reminder that our therapies remain inadequate.

In contrast to most other rheumatology (or other specialty) meetings reviewed on Medscape, the IHSS represents one of the few symposia attended by multiple disciplines, regulatory agencies, pharmaceutical representatives and patient advocacy groups.

As rheumatologists seldom attend clinical or research meetings of other health care specialties, and we rarely read their journals, we do not

appreciate their guidelines for diagnosis and therapy. Thus, this unique conference provides a unique opportunity for interdisciplinary coordination of diagnosis, therapy and collaborative research. Although rheumatologists speak the same “language” as other clinical and regulatory agencies, it was soon apparent that rheumatologists speak a different “dialect.” Thus, this symposium allowed direct discussions about prevalent misconceptions in each specialty.

The meeting was attended by over 350 medical specialists representing over 35 countries on 5 continents. This international “tour de force” was organized by Alan Baer (Rheumatology) and Esen Akpek (Ophthalmology) of Johns Hopkins Medical School (Baltimore), and Ilias Alevios of National Institutes of Health (NIH, Bethesda, Maryland). The IHSS was organized in coordination with the SSF by virtue of the extraordinary efforts of Kathy Hammitt and Steven Taylor, who continually brought the meeting back to our fundamental objective of optimizing patient care.

In addition to the 35 invited international expert speakers in the field of SS, the audience was treated to cutting edge technology and treatments by world renown members of Johns Hopkins faculty and regulatory agencies including the Food and Drug Administration (FDA) also located in nearby Bethesda. This is an important point, as rheumatologists and other clinical specialties endeavor to coordinate diagnostic and therapeutic guidelines that will lead to drug approval.

It was clear from the start that SS patients may be the rheumatologist’s worst nightmare. As the time per patient visit becomes more limited, the patient turns to the rheumatologist for everything from precautions at time of surgery to interpretation of laboratory studies by other specialists. In their frustration with the complex medical system, the SS patient has already researched and gathered misinformation from blogs on the Internet.

Indeed, it seems to the rheumatologist that many other medical specialties end their patient interaction with the instruction, “ask your rheumatologist about this.”

II. Summary of Topics Clinically Relevant for Medscape Readers

a. Have the international experts finally agreed on a diagnostic criteria that will serve as a basis for criteria of primary SS?

Yes, we now have a working criteria that is acceptable to regulatory Agencies [1]. However, the criteria are still imperfect and new modalities such as ultrasound or biomarkers may lead to revised future criteria.

b. Using the current criteria to identify a uniform group of patients, what have we learned about genetic, epigenetic, proteomics and environmental factors?

The group that we clinically identify as SS is quite heterogeneous in clinical features, and these subgroups have particular proteomic and epigenetic signatures. In particular, subsets of SS patients were identified on the basis of the interferon type 1 and type 2 gene signatures [2].

Most papers recognized 3 subgroups: interferon negative signature, type 1 IFN signature, and type 1 plus type 2 IFN signature. Surprisingly, an elevated ESSDAI was found in each subgroup. The only domain that was consistently different was elevated “biologic marker” domain in the IFN1 plus IFN2 subgroup. The type 1 IFN signature subgroup remained stable over time, while the other subgroups showed periodic variations.

Fatigue and patient reported outcome was spread over all three subsets.

c. After the dramatic success of biological agents in rheumatoid arthritis, and psoriatic arthritis, where do we stand in SS in therapeutic trials?

The “successes” in SS patients with extraglandular manifestations including mixed cryoglobulinemia, hemolytic anemia, vasculitis and lymphoproliferative manifestations were reviewed by Wallace (Los

Angeles) and others. These studies including agents such as rituximab, abatacept and epratuzumab were reviewed. However, the “benign” manifestations such as objective measurements of dry eyes, dry mouth, fatigue and cognitive changes were not significantly changed in comparison to placebo (which included pre-infusion corticosteroids).

There was been considerable excitement about CFZ533, a monoclonal antibody to CD40 ligand that has a “silent” Fc receptor; this antibody does not have thromboembolic complications and does not deplete B-cells[3, 4].

The SS patients enrolled in these trials (3 different dosing regimens)(papers presented by Pappas from Boston and Fisher from London) had high ESSDAI scores since the end point was a 3 point improvement in these scores. However, only about 10% of the total SS patient population patients exhibit this very high disease activity. Future studies will be required to see if beneficial effects are noted in the vast majority of patients with “benign” symptoms.

- d. Given our large number of consecutive therapeutic failures for “benign” symptoms of SS, are we targeting the correct pathways?

Indeed our consecutive therapeutic failures in the majority of SS patients (ie. those with benign symptoms), suggests that we are not yet addressing the more subtle pathways of secretory and autonomic function (dry eyes, dry mouth) as well as other hypothalamic axis abnormalities[5].

- e. ***What are newest approaches to conservative therapy for dry eyes***

World leaders in Ophthalmology pointed out the frequently overlooked role of *meibian gland dysfunction (MGD)*(Sullivan, Boston; Koh, Boston). *This deficient production of lipids that retard tear film evaporation are present in the majority of SS patients [6]. Treatment modalities may include a brief course of antibiotics (doxycycline or azithromycin)[7] or a pulsed thermal pulsation[8, 9].*

f. What are the new approaches to dry mouth?

Oral Medicine experts shared their suggestions for both caries prevention and treatment of oral dryness symptoms (Pappas, Boston)[10].

Mucins also play a key role in improving viscosity of the buccal mucosa and the patient's perception of dryness. Although this has been recognized for over 50 years, the development of acceptable oral saliva substitutes has been slow[11, 12]. Although muscarinic agonists (cevimeline, pilocarpine) have some benefit, further therapies are needed.[13] Recent trials with glycerol derivatives suggest a potential future role[13].

Symptoms of oral discomfort may result from low-grade yeast infections and others with "burning mouth" syndrome may be a form of oral neuropathy, as well as a manifestation of depression.

g. Why is there such a discordance between patient self described ocular symptoms and objective findings?

It was surprising for rheumatologists to learn that "best corrected vision" which is done with a high contrast visual chart is not a good measure of the patient's symptoms. As usually, performed the patient looks at the vision chart shortly after instilling their eye drops. In real life, their ability to detect "contrast" is strongly dependent on the tear film and rapidly deteriorates in time after the initial blink (Koh, Boston).

h. Have particular viruses or alterations in the biome been causally linked to pathogenesis of SS.

Indirect evidence continues to link Epstein virus infection, since the parotid gland is a site of latency and periodic reactivation. However, it is difficult to assess a causative role since EBV infection and latency is ubiquitous in normal individuals. An interesting particular

link may be the finding of microRNA's (miRNA) with sequence similarity to EBV in glandular cells lacking other evidence of active EBV infection[14-16].

The biome includes the mucosal membranes of the mouth that are influenced by periodontal disease, as well as the microbial antigens of the intestine. Since many of these organisms are not easily cultured, next generation sequencing will be required to assess their role in shaping the immune repertoire and SS pathogenesis[17].

III. Conclusions

SS represents an opportunity for clinical and basic research at the frontier of a multi-disciplinary disorder. At a time when we are flooded with new therapies for RA and its related disorders, the challenge of SS and its closely related disorder of systemic lupus erythematosus (SLE) is a challenge worthy of our years of training to be rheumatologists.

SS is a “symptom” complex that is due to infiltrative lymphocytic disorder. It has close overlap with systemic lupus erythematosus in its genetic, clinical and therapeutic properties. However, it is easiest to think of SLE as predominantly an antibody and immune complex disorder (ie. glomerulonephritis, hemolytic anemia, pleural effusions) while SS is more characterized by its high frequency of lymphoma and infiltrative neuropathies. Nevertheless, over 50% of SS patients with dry eye symptoms are misclassified as SLE even in rheumatology departments with excellent experience with SS [18].

The 14th IHSS provided opportunity to improve patient identification, subset patients by biomarkers, and thus rationally develop therapies based on the tools of “personalized medicine.”

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