Updates in Sjögren Syndrome

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A Multidisciplinary, Multiagency Meeting

The 14th International Sjögren's Symposium was held April 18-21, 2018, in Washington, DC. Experts in ophthalmology, oral medicine, rheumatology, internal medicine, neurology, radiology, pathology, and basic research gathered at this interdisciplinary meeting to discuss diagnostic and clinical advances from the past 3 years. In addition, speakers from the US Food and Drug Administration and the pharmaceutical industry presented guidelines and pathways forward to drug approval.

Patients with Sjögren syndrome (SS) and their national patient organization, Sjögren's Syndrome Foundation, were present to express their concerns about the impact of SS on their quality of life and to serve as a reminder that our therapies remain inadequate.

In contrast to most other rheumatology meetings reviewed on Medscape, this symposium represents one of the few that are attended by practitioners of multiple disciplines, regulatory agencies, pharmaceutical representatives, and patient advocacy groups. This symposium provided a unique opportunity for interdisciplinary coordination of diagnosis, treatment, and collaborative research, and allowed direct discussions about prevalent misconceptions in each specialty.

This international tour de force was organized by Alan Baer and Esen Akpek, from Johns Hopkins University School of Medicine, and Ilias Alevizos, from the National Institutes of Health, in coordination with Sjögren's Syndrome Foundation, 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. More than 350 medical specialists were in attendance, representing 35+ countries on five continents, and they were treated to presentations on cutting edge technology and treatments by world-renowned members of Johns Hopkins faculty and regulatory agencies.

It was clear from the start that people with SS may be the rheumatologist's most difficult patients. Patients with SS turn to their rheumatologists for everything, from precautions at the time of surgery to interpretation of laboratory studies performed by other specialists. In their frustration with the complex medical system and limited time per patient visit, patients are researching and gathering misinformation from blogs on the Internet.

Indeed, it seems to the rheumatologist that many other medical specialists end their patient interaction with the instruction, "Ask your rheumatologist about this."

Summary of Clinically Relevant Topics

Diagnostic Criteria for Primary SS

We now have working criteria that are 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.

Genetic, Epigenetic, and Proteomic Factors

SS is quite heterogeneous in clinical features, and subgroups of patients with SS have proteomic and epigenetic signatures. In one study,[2] subsets of patients were identified on the basis of the interferon (IFN) type 1 and type 2 gene signatures: interferon negative signature, type 1 IFN signature, and type 1 + type 2 IFN signature. Surprisingly, an elevated EULAR Sjögren's syndrome disease activity index (ESSDAI) score was found in each subgroup. The only domain that was consistently different was the elevated "biologic marker" domain in the IFN1 + IFN2 subgroup.

The type 1 IFN signature subgroup remained stable over time, but the other subgroups showed periodic variations. Fatigue as a patient-reported outcome was spread over all three subsets.

Therapeutic Trials in SS

The successes seen with the use of biologic agents in patients with SS who have extraglandular manifestations, including mixed cryoglobulinemia, hemolytic anemia, vasculitis, and lymphoproliferative manifestations, were reviewed.[3] These studies included agents such as rituximab, abatacept, and epratuzumab. Objective measurements of benign manifestations of SS, such as dry eyes, dry mouth, fatigue, and cognitive changes, were not significantly improved with these agents compared with placebo (which included preinfusion corticosteroids).

CFZ533, a monoclonal antibody to CD40 ligand that has a silent Fc receptor,[4] has caused considerable excitement. This antibody does not cause thromboembolic complications and does not deplete B cells.[4,5]

The patients enrolled in clinical trials had high ESSDAI scores; the endpoint was a 3-point improvement in score. However, only about 10% of the total SS patient population exhibits this very high disease activity. Future studies will be required to see if beneficial effects are noted in the vast majority of patients with milder symptoms.[6,7]

Targeting the Correct Pathways

The consecutive therapeutic failures in the majority of patients with SS (ie, those with benign symptoms) suggest that we are not yet addressing the more subtle pathways of secretory and autonomic function (dry eyes, dry mouth) as well as other abnormalities of the hypothalamic axis.[8]

World leaders in ophthalmology pointed out the frequently overlooked role of meibomian gland dysfunction. The majority of patients with SS have this deficient production of lipids that retard tear film evaporation.[9] Treatment modalities may include a brief course of antibiotics (doxycycline or azithromycin)[10] or thermal pulsation.[11,12]

Experts on oral medicine shared their suggestions for both caries prevention and treatment of dry mouth.[13] Mucins play a key role in improving viscosity of the buccal mucosa and the patient's perception of oral dryness. Although this has been recognized for more than 50 years, the development of acceptable oral saliva substitutes has been slow.[14,15] Muscarinic agonists (eg, cevimeline, pilocarpine) have some benefit, but additional therapies are needed.[16,17] Recent trials with glycerol derivatives suggest a potential future role.[18]

Symptoms of oral discomfort may also result from low-grade yeast infections, and burning mouth syndrome may be a form of oral neuropathy or a manifestation of depression.

Patient-Described Ocular Symptoms vs Objective Findings

Rheumatologists were surprised to learn that best-corrected visual acuity, which is measured with a high-contrast visual chart, is not a good measure of the patient's symptoms. As commonly performed, the patient looks at the vision chart shortly after having eye drops instilled. In real life, the patient's ability to detect contrast is strongly dependent on the tear film, which rapidly deteriorates after blinking.

The Pathogenesis of SS

Indirect evidence continues to link Epstein-Barr virus (EBV) infection with SS, because the parotid gland is a site of latency and periodic reactivation. However, a causative role is difficult to assess because EBV infection and latency are ubiquitous in normal individuals. An interesting link may be the finding of microRNA with sequences similar to those of EBV in glandular cells lacking other evidence of active EBV infection.[19-21]

The biome includes the mucosal membranes of the mouth, which are influenced by periodontal disease, as well as the microbial antigens of the intestine.[22] Because 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.

Conclusions

SS represents an opportunity for clinical and basic research at the frontier of a multidisciplinary disorder. At a time when

we are flooded with new therapies for rheumatoid arthritis and its related disorders, the challenge of treating patients with SS is one worthy of our years of training to be rheumatologists.

SS is a symptom complex that is due to an infiltrative lymphocytic disorder and has close overlap with systemic lupus erythematosus (SLE) in its genetic and clinical properties. Almost half of patients with SS who have dry eye symptoms are misdiagnosed with SLE, even in rheumatology departments with experience managing SS.[23] It is easiest to think of SLE as an antibody and immune complex disorder that causes such conditions as glomerulonephritis, hemolytic anemia, and pleural effusions, whereas SS is more characterized by its high frequency of lymphoma and infiltrative neuropathies.

The 14th International Sjögren's Symposium provided an invaluable opportunity to improve the identification of subsets of patients by utilizing biomarkers and rationally develop therapies based on the tools of personalized medicine.

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