

- 5** SSF Awards New Grants
- 7** Clinical & Industry News
- 17** SSF In Action
- 19** Patient Education: Clinical Trials - Getting Involved

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Starting a Clinical Trials Program



Herbert S. Baraf, MD, FACP, MACR

Herbert S. Baraf, MD, FACP, MACR
 Arthritis and Rheumatism Associates, P.C.,
 Wheaton, Maryland

The Sjögren's Syndrome Foundation has been a lightning rod for patients looking for better treatments as well as for pharmaceutical companies looking for investigators and patients to help develop new therapies. A recent visit to www.ClinicalTrials.gov was instructive. Using the search term "Sjögren" I found 66 projects. Many of these focused on potential therapies for Sjögren's. Most were multi-center trials sponsored by pharmaceutical companies. Of the 66 "hits," 20 of the trials were actively enrolling patients in the United States.

Developing new therapies creates an enormous challenge for companies to identify qualified investigators who understand Sjögren's and who regularly see these patients. Pharmaceutical companies frequently contact the Foundation to connect with the Sjögren's community of physicians and patients. Thus, rheumatologists who perform clinical trials are in demand, and rheumatologists who don't perform clinical trials have an opportunity to develop a

Continued on page 2 ▼

SSF 5-Year Breakthrough Goal Update



Steven Taylor, SSF CEO

I'm honored and excited to share that the SSF has exceeded our Breakthrough Goal: to shorten the time to diagnose Sjögren's by 50% in five years. The SSF embarked on this ambitious 5-year goal in 2012, a point when the average time for a patient to receive an accurate diagnosis was nearly six years. To achieve our goal, we needed to shorten the diagnosis time to less than three years. Today, the new average time to diagnosis is 2.8 years!

From the beginning, we understood our goal of reducing the time to diagnosis by 50% may be ambitious, however, we knew how important an undertaking it was to help the many patients suffering from symptoms but with no definitive diagnosis. We knew this goal could be transformative, and that buy-in, education and awareness among physicians and health care providers would be key to its success. These efforts to increase awareness and education in the health care community also served to improve the care of patients who had already been diagnosed with Sjögren's.

Diagnosing a patient with Sjögren's, let alone quickly, is challenging. Often times, this can be because a patient may see a variety of providers, such as a primary care physician, dentist and gynecologist, and discuss specific symptoms with each, but not the entirety of what they're experiencing. Alone, each symptom may not indicate an underlying autoimmune disease, but when considered together, could suggest Sjögren's.

Continued on page 6 ▼

"Clinical Trials" Continued from page 1 ▼

research program in their practices and become engaged.

In a previous discussion, which can be found in Vol. 12, Issue 3 of *Sjögren's Quarterly*, I outlined the benefits that I've personally experienced being a clinical investigator over four decades of practice. These benefits are numerous, ranging from satisfaction of providing patients with new treatment options on one hand to professional growth and intellectual stimulation on the other. Many physicians have thought about doing clinical trials but are uncertain of what they need to do to get involved.

As every rheumatologist knows, there has been a virtual explosion of drug development in rheumatology, not just for Sjögren's but for almost every category of disease we treat. The "pipeline" for new therapies is bursting at the seams. Further, drugs that are already on the market are often restudied for new indications or formulations. In short, the demand for physician investigators is sure to be sustained.

So, if you are interested in becoming a clinical investigator, how do you get started? How do you get involved in clinical research? I have some suggestions on becoming a clinical investigator and will outline the basic pre-requisites. My perspective is that of a private practitioner in a single specialty rheumatology practice. Physicians practicing in virtually any setting can successfully perform trials, so view my ideas generically whether you are a private practitioner, an academician, an employee of a large health system or a member of a multispecialty practice.

Successful investigators all have a few things in common. They share a drive to do this kind of work. They have space in which to see patients, store drugs, supplies and records. These physicians usually have a patient base from which to recruit participants for trials, have

an identified staff member who can serve as a study coordinator and a quiet area for that coordinator to review and process documents.

Clinical trial participants are typically recruited from within an investigator's own practice, but reaching out to the community through advertisements or to colleagues through personal contacts and letters may help an investigator find eligible subjects for the trials that they are performing. Sponsors often have their own recruitment strategies to identify patients, which can help with study enrollment.

Selecting a coordinator is critical to creating a foundation for doing clinical trials. A nascent coordinator preferably has had experience working with patients and has familiarity with the disease entity being studied, though understanding the disease under investigation can be taught to an aspiring coordinator. Seek out an individual who is meticulous, precise, accurate in charting, responsible and capable of critical thinking. You may already have such a person on your staff.

Every seasoned clinical investigator began their career with a first study. Every successful investigator learns with each subsequent study they conduct, and they become more sophisticated and more proficient. I began with one study and after 35 years have done over 400. But it started with a first trial. As I gained experience, I grew as an investigator, but I knew enough when I started to successfully complete my first trial. You must be inquisitive, interested in the process, humble, open, willing to learn, earnest, careful and ethical in your conduct. These are not just characteristics of a clinical trialist, they are the critical characteristics of a good clinician.

Once an infrastructure begins to take form, the next hurdle an investigator must overcome is landing that first study. This is where the budding physician investigator needs to use his or her social skills. There are many avenues to pursue to find opportunities, among them:

- networking with colleagues that have done clinical trials
- attending presentations of new therapies at national and regional meetings where you can express your interest in participating in present or future trials with the presenter or the sponsoring company
- exploring online websites such as www.clinicaltrials.gov or www.centerwatch.com that provide information on clinical trials by therapeutic category
- reaching out to pharmaceutical sales representatives to refer you to the clinical development team at their companies

Should a sponsor show interest in you as an investigator, they will usually call to set up a site visit. A clinical

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Continued on page 4 ▼

NEUTRASAL® RELIEVES DRY MOUTH SYMPTOMS SO SJÖGREN'S PATIENTS HAVE

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- Solution should not be swallowed but be spit out.
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REFERENCE: 1. Levin EZ. The beneficial effects of a supersaturated calcium phosphate rinse on the oral cavity in xerostomia patients. Tulsa, OK: PennWell publications; 2014.

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"Clinical Trials" Continued from page 2 ▼

research associate (CRA) and perhaps other members of the sponsor's team would usually make an appointment to visit your facility. When they visit, they will assess your ability to conduct research. They will want to meet your coordinator. They will discuss the protocol with both you and the coordinator and review study design, the inclusion and exclusion criteria, and other aspects of the investigative plan. They will be particularly interested in determining if you have patients who would be appropriate for the project and if you have a patient recruitment plan.

At the site visit, the CRA will also check out the space where you intend to do the study, look at where the drug will be kept and where records will be stored. Your interaction with the CRA, the questions you ask and the representations you make will enable the sponsor to determine your suitability as an investigator.

Once your site is selected for a clinical trial and before you see your first patient, there will be much preparatory work to be done. The sponsor will send you the final protocol to review, an investigational brochure (a comprehensive document summarizing the body of information about the investigational product), a copy of the proposed informed consent document and a budget.

The final protocol, investigational brochure and the informed consent should all be carefully reviewed. You may wish to make some changes to the informed consent for your site and should review these changes with the sponsor. Once finalized, you will need to submit these three documents to an Institutional Review Board (IRB) for review and approval. An IRB is an organization mandated to protect the rights and ensure the safety of individuals as subjects of clinical research. Boards are composed of at least five members including scientists, physicians and lay people. An IRB may be centrally contracted by the sponsor to provide service to all sites performing the trial, or you may need to find your own IRB to review and approve the study plan and informed consent. Don't worry – there are many IRB's locally and nationally that are experienced in reviewing protocols, possibly even one in the hospital with which you are affiliated.

Familiarizing yourself with Good Clinical Practices (GCPs) including standards related to presenting an

informed consent to a potential trial participant is critical for the safe and ethical conduct of a clinical trial. There are numerous resources available that discuss GCP's and can provide a practical guide to this critically important aspect of clinical trial implementation. The IRB, the sponsor and the FDA are all keenly focused on the investigator's adherence to the investigational plan and compliance with principled standards of subject protection.

Conducting clinical trials is very different from caring for patients in a medical practice. Following the investigative plan to the letter is paramount. Physician and patient conduct in a clinical trial are of equal importance. Simple things like the patient's drug compliance, adhering to required "visit windows", monitoring changes in concomitant medications, recording details of intercurrent illnesses, reporting serious adverse events, and documenting your review of laboratory results are all central to the proper conduct of a clinical trial, to name just a few. In addition to all of this, maintaining standards of excellent patient care is essential.

Remember that most trials focus on determining the efficacy and safety of new drugs in equal measure. Patient comfort and safety are always paramount, but so is the integrity, timeliness and accuracy of data capture.

I have presented a practical but simple guide to enter the world of clinical trials. It is by no means an exhaustive discussion of the clinical trials process. Once you become engaged, your sophistication will grow with every trial you do. If you conduct your work competently and with integrity you will be in demand. What starts as a small initial effort can grow into a full-fledged program. With that growth, you will learn things along the way that will make you a better physician, a smarter and more "plugged in" clinician and a better manager. You will also become a member of a rewarding association of physicians, coordinators and researchers. Your professional life will be enriched by those relationships and by the knowledge that your patients will benefit from your professional growth. You will be confident in your ability to offer all your patients the most current advances in therapy, whether in your trials program or as a result of the success of new therapies developed with your input. ■

Please contact us at sq@sjogrens.org if you currently engage in clinical trials or are interested in doing so.

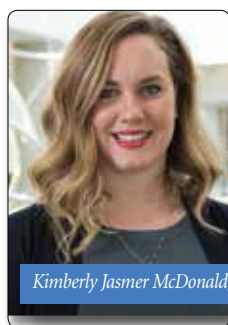




SSF Awards 2018-2019 Research Grants

The Sjögren's Syndrome Foundation is excited to announce the selection of the 2018-2019 research grant recipients. After careful consideration of this year's outstanding pool of applicants, the research review committee has awarded four new research grants and renewed three excellent research grants from the 2017-2018 awardees.

2018-2019 Research Grant Recipients



Kimberly Jasmer McDonald, PhD

Kimberly Jasmer McDonald, PhD
Postdoctoral Fellow, University of Missouri, Dept. of Biochemistry, Columbia, MO

Research Project
P2Y₂ Receptor as Therapeutic Target in a Sjögren's Syndrome Mouse Model

Abstract

Sjögren's is a chronic autoimmune exocrinopathy characterized by lymphocytic infiltration of the salivary and lacrimal glands. Chronic inflammation leads to salivary gland dysfunction and systemic effects including fibrosis, secondary autoimmune diseases, and lymphoma development. Using the NOD.H-^{2h4},IFN γ ^{-/-},CD28^{-/-} mouse model of Sjögren's, we explore the contributions of P2Y₂R-mediated inflammation to the Sjögren's phenotype. Our preliminary findings demonstrate that P2Y₂R antagonism improves salivation and diminishes inflammation in the submandibular gland (SMG). Additionally, functional P2Y₂R is expressed in SMG B cells. Through the nucleotide activation of P2Y₂R on infiltrating SMG B cells and subsequent chemokine and cytokine release, we hypothesize that P2Y₂R might facilitate the recruitment of peripheral lymphocytes leading to salivary gland destruction, hyposalivation, and chronic inflammation. It is the goal of this proposal to elucidate the role P2Y₂R plays in infiltrating SMG B cell function and evaluate P2Y₂R as a novel therapeutic target for the treatment of Sjögren's.



Melodie Lynn Weller, PhD

Melodie Lynn Weller, PhD
Assistant Professor, University of Utah, School of Dentistry, Salt Lake City, UT

Research Project
The Impact of a Global Increase in Hepatitis Delta Virus (HDV) Exposure on the Incidence of Sjögren's Syndrome Diagnosis

Abstract

A viral infection has thought to be one of the triggers in the development of Sjögren's. Recently, we identified hepatitis delta virus (HDV) in Sjögren's salivary gland tissue and demonstrated the capacity of HDV to trigger a complete disease phenotype in vivo. Our focus now is to define how patients are being exposed to HDV. Preliminary HDV epidemiological studies have identified a significant increase in diagnosis across three continents and are suggestive of a change in viral transmission patterns. We hypothesize that this increase in global HDV exposure may lead to increased Sjögren's development in susceptible populations. This discovery in connection with the novel HDV profile observed in Sjögren's patients is highly innovative and warrants immediate investigation. Therefore, we have designed two studies to perform cross-correlative analysis between HDV and Sjögren's diagnoses within the Utah population. These studies will provide the foundation for advancement to clinical trials.

Continued on page 8 ▼

"5-Year Breakthrough Goal" Continued from page 1 ▼

The Foundation's hope remains that Sjögren's is top-of-mind for physicians when a patient complains of dry mouth, dry eye, fatigue or joint pain. Many of you reading this may be aware that the Foundation's awareness efforts have and continue to work on educating all medical specialties, as well as the general public, on knowing and being able to identify Sjögren's symptoms. An early diagnosis and the appropriate management and treatment are important for helping to prevent serious complications and can greatly improve a patient's quality of life. Without the appropriate care, patients can experience a wide array of serious issues, including corneal scarring, tooth loss, misdiagnosed neuropathy pain, internal organ involvement, profound fatigue, chronic respiratory problems, and more.

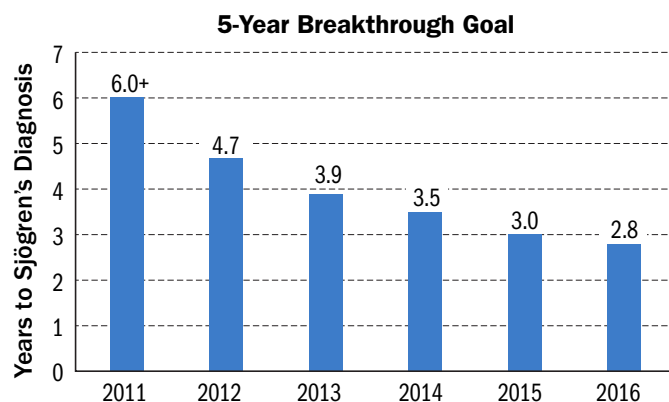
Beyond the physical manifestations of the disease, we know that the emotional burden of having an undiagnosed or misdiagnosed disease can be heavy. The Foundation has heard from many patients who share their daily struggle and worries about what was wrong with them before they were diagnosed and the validation they eventually felt when they had finally received an explanation for their symptoms.

In addition to sharing this momentous news, I wanted to briefly share what took place over the past five years to reach where we are today.

History of the 5-Year Breakthrough Goal

From the inception of this goal, the Foundation worked with Polaris, a marketing research company, who surveyed newly diagnosed patients in the U.S. in each of the five years of this initiative. The data was then analyzed and provided to the Foundation, showing the time it took for patients to receive a proper diagnosis of Sjögren's. Using the original data, collected in 2012, as a benchmark, subsequent progress and a steady decline could be seen over the course of this initiative. Figure 1 details this progress.

Figure 1.



Additional information collected by Polaris was used by the SSF Breakthrough Goal Committee to inform three specific action items, each with sub-goals, all of which helped to achieve the ultimate goal of reducing the time to diagnosis. Each year, priorities were placed as sub-goals under the three action items, which helped to focus our combined efforts.

These three action items, which remained consistent throughout the initiative, were: increase public awareness; increase involvement from the Foundation's friends and partners; and increase education and awareness among health care professionals.

The large majority of subscribers of *Sjögren's Quarterly* are health care professionals, representing many different specialties, so this last action item is particularly relevant to the readers here. Of note, the sub-goals that were included under this action item in the final year of the initiative were:

- Increase education and awareness among rheumatologists
- Build strong relationships with the top professional areas that treat Sjögren's patients
- Continue to develop clinical practice guidelines and promote their use by clinicians
- Ensure that the Foundation is positioned as the go-to source for healthcare professionals for Sjögren's information
- Ensure that our professional materials are meeting healthcare professional needs

Today, the SSF Board of Directors and staff are humbled by the support of the patients, providers and corporate partners for all of the help and encouragement throughout the duration of this work to get to where we are today. We knew it wouldn't be easy to achieve this goal and our accomplishment is remarkable. With the help of many, the dream of making Sjögren's a household name is within our grasp.

Although our job is far from done, the SSF has seen our years of hard work and perseverance paying off. The Foundation will continue to fight for all patients and is committed to supporting the accelerated development of improved diagnostics, management approaches and therapeutics for the purpose of improving the quality of life for all Sjögren's patients. Early in the new year the Foundation will announce a new, ambitious, Breakthrough Goal. Stay tuned.

On behalf of the SSF, thank you for all you do and your continued support of the Foundation and the Sjögren's community. ■



Clinical News: Rheumatology

Incidence and Prevalence of Sjögren's in New York County, NY

Investigators have determined the incidence and prevalence of Sjögren's in New York County, NY, to be 3.5 and 13.1 per 100,000 person years, respectively. These estimates were made using the Manhattan Lupus Surveillance Program (MLSP), a population-based retrospective registry of cases of systemic lupus erythematosus and related diseases, including Sjögren's. The MLSP includes cases identified from hospitals, rheumatologist and population databases and capture-recapture analyses was used to account for under-ascertainment of cases. After capture-recapture adjustment the incidence and prevalence increased to 4.1 and 14.2, respectively. Notably, the incidence was highest in non-Latina Asian women (10.5) compared to White women (6.2), non-Latina Black women (3.3) and Latina women (3.2). There were no differences in prevalence when comparing race and ethnicities.

Citation:

Izmirly PM et al. The incidence and prevalence of adult primary Sjögren's syndrome in New York County. *Arthritis Care Res (Hoboken)*. 2018 Jul 25. doi: 10.1002/acr.23707. [Epub ahead of print].

No Association Found Between Use of Biologics and Preterm or SGA Births

Researchers have found no association between the use of biologics before and during pregnancy with an increased risk of preterm delivery or small-for-gestational age (SGA) births. In total, 109 women, accounting for 120 pregnancies, met the inclusion criteria, which required a minimum of three months of exposure to biologics, either before or during pregnancy. An unadjusted analysis resulted in ORs of 1.64 (95% CI

1.02 to 2.63) for preterm deliveries and 1.34 (95% CI 0.72 to 2.51) for SGA. When matched to 600 unexposed pregnancies the OR for the association of biologics exposure and preterm deliveries changed to 1.13 (95% CI 0.67 to 1.90) and to 0.91 (95% CI 0.46 to 1.78) for SGA.

Citation:

Tsao NW et al. Risk of preterm delivery and small-for-gestational age births in women with autoimmune disease using biologics before or during pregnancy: a population-based cohort study. *Annals of the Rheumatic Diseases* 2018; 77:869-874.

Effect of Smoking on Disease Characteristics and Cytokine Levels in Sjögren's Patients

A comparison between Sjögren's patients (n=51), which included those who have ever or never smoked, and controls (n=33) found significant differences in the expression of cytokines IL-6, IL-12, IL-17 and IL-18, which were significantly increased in Sjögren's patients. No differences were found in Sjögren's patients between smokers and non-smokers except between TNF- α . A negative association between patients who had ever smoked and a positive lip biopsy was found, which supports previous research findings. As part of this study, investigators assessed the following serum cytokines: IL-1 β , IL-2, IL-3, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, IL-33, IFN- α , IFN- γ , TNF- α , EGF, BAFF, Fas-ligand, RANTES and TGF- β 1.

Citation

Olsson P et al. Smoking, disease characteristics and serum cytokine levels in patients with primary Sjögren's syndrome. *Rheumatology International*. doi: org/10.1007/s00296-018-4063-8

Impact of Smoking and SES on Risk for Sjögren's Diagnosis

An investigation into the impact of smoking and socioeconomic status on the risk of a subsequent Sjögren's diagnosis found significant associations between a reduced risk with current smoking activity (OR 0.3; 95% CI 0.1-0.6) and an increased risk with former smoking activity (OR 4.0; 95% CI 1.8-8.8). Socioeconomic status

"SSF Grants" Continued from page 5 ▼



Yee Ling Wu, PhD

Yee Ling Wu, PhD

Assistant Professor, Loyola University Chicago, Dept. of Microbiology and Immunology, Maywood, IL.

Research Project

Genetic and Phenotypic Polymorphisms of Complement C4 in the Pathogenesis of Sjögren's Syndrome

Abstract

Low levels of complement C4 protein are often observed in Sjögren's and are associated with cryoglobulinemia and lymphoma. Genetic deficiency and low gene copy numbers of complement C4 have been shown to be an important risk factor for lupus. Activation of C4 protein during inflammation consumes C4 protein and mediates tissue injuries. We hypothesize that C4 genetic and protein polymorphisms are engaged in disease predisposition and in modulating the clinical presentation of Sjögren's. We will analyze patient samples using accurate molecular assays for determining C4 gene copy numbers, immunoassays for activated complement protein products and transcriptomic analyses to 1) determine the cause of low C4 in Sjögren's, and 2) evaluate the utility of combining genetic stratification of C4 and new protein markers in the diagnosis and management of Sjögren's.



John Robert Kelly, DDS, MS, DMedSc

John Robert Kelly, DDS, MS, DMedSc

Professor, UCONN Health, Farmington, CT

Research Project

Artificial Salivary Gland Dental Implant Development

Abstract

Our research group proposes to treat xerostomia with an implantable device for continuous relief of chronic dry mouth through the development of a dental implant to harvest and filter the self-renewing fluid within the marrow space of the jaw bone and to release the filtered fluid into the mouth as substitute saliva. We proposed design, test and refinement prototypes of this implant system. Much of the work will be done at 3-5x scale with the intention of future miniaturization to anatomic size. This work will emphasize the primary

performance requirement of repetitively pumping fluid through the implant at force consistent with tooth contact and mastication. Milestones include design, prototype and testing with at least 0.2-0.3 ml/min drawn from bone marrow space analogues.

Renewed 2017-2018 Research Awards

Anat Galor, MD, MSPH

Associate Professor of Clinical Ophthalmology, Bascom Palmer Eye Institute, University of Miami, Miami, FL.

Research Project

Fecal Microbiota Transplant in Sjögren's Syndrome

Description

This study aims to study the feasibility and efficacy of fecal microbiota transplant (FMT) in Sjögren's patients, particularly, whether FMT can improve the dry eye phenotype.

Daniela Cihakova, MD, PhD

Associate Professor of Immunology; Associate Director of Immunology Laboratory; Director of WHO Collaborating Center, Dept. of Pathology, Johns Hopkins University, Baltimore, MD

Research Project

Epithelial Cells and Innate Lymphoid Cells' Collaborative Role in the Pathogenesis of Primary Sjögren's Syndrome

Description

This translational project aims to investigate the pathogenic features of salivary epithelial cells and innate lymphoid cells on Sjögren's in humans and murine models and has the potential to lead to new therapeutic and diagnostic approaches.

Danielle Marie Robertson, BS, OD, PhD

Associate Professor, University of Texas Southwestern Medical Center, Department of Ophthalmology, Dallas, TX

Research Project

Comparative Structural and Molecular Analysis of Tear and Salivary Derived Exosomes in Sjögren's Syndrome

Description

This project is testing the hypothesis that saliva and tear derived from exosomes will contain biomarkers unique to patients with Sjögren's. This hypothesis is being tested by characterizing the ultrastructural biology and molecular signature of saliva and tear derived exosomes from women with Sjögren's compared to age-matched healthy controls using cryo-electron microscopy and next generation RNA-sequencing. ■

"Clinical News" Continued from page 7 ▼

and education had no significant impact on the risk of a subsequent Sjögren's diagnosis. The authors believe additional studies are necessary to further investigate whether this is a reflection of the biological effect of smoking or other mechanisms. This study included 63 Sjögren's patients and additional matched controls identified from two large population based health surveys and later linked to the Malmo Sjögren's Syndrome Register.

Citation

Olsson P, Turesson C, Mandl T, Jacobsson L & Theander E. Cigarette smoking and the risk of primary Sjögren's syndrome: a nested case control study. *Arthritis Res Ther*. 2017 Mar 7;19(1):50. doi: 10.1186/s13075-017-1255-7.

IgA RF as a Predictive and Diagnostic Marker for Sjögren's

Sjögren's patients (n=77) were found to have significantly higher levels of IgA rheumatoid factor (RF) compared to a group with idiopathic sicca symptoms (n=37). IgA RF was found to be associated with xerostomia, severe sialoscintigraphic grade, low unstimulated salivary flow rates, antinuclear antibody, high IgG and IgM/G RF and low levels of C3 in Sjögren's patients. For Sjögren's diagnosis, IgA RF had a sensitivity of 83.1%, a specificity of 78.4%, a positive predictive value of 88.9% and a negative predictive value of 69.0%. Positive correlations were found between IgA RF and sialoscintigraphic grade and IgG while negative correlations were found between IgG/M and unstimulated salivary flow

rate and C3 levels.

These findings confirm the potential for IgA RF to distinguish Sjögren's from idiopathic sicca symptoms and support that IgA RF should be the predictive and diagnostic marker in Sjögren's patients. For this study, investigators used ELISA to measure RF levels and receiver operating characteristic curves to determine and compare the diagnostic accuracy of IgA RF to other diagnostic tests.

Citation

Lee KA et al. Clinical and diagnostic significance of serum immunoglobulin A rheumatoid factor in primary Sjögren's. *Clin Oral Invest* (2018). doi.org/10.1007/s00784-018-2545-4.

Morphological Differences Related to Serological Variables: Comparing Sjögren's and Sjögren's Accompanied by Scleroderma.

To investigate the morphological differences in relation to serological variables between Sjögren's patients and patients with scleroderma and Sjögren's, researchers examined serum autoantibody information and evaluated minor salivary gland biopsies, lymphocyte focus scores, plasma cell focus scores and fibrosis rates. Investigators found that for Sjögren's patients (n=43), 16 cases (37%) were positive for both biopsy and autoantibody, 25 cases (58%) were positive for biopsy alone and one case (2%) was positive for autoantibody alone. For patients with scleroderma and Sjögren's (n=26)

Continued on page 10 ▼



Updates to the SSF Research Program!

The SSF strives to foster research that will have the greatest potential impact on Sjögren's patients and supports the research community through research grants, placing a high priority on clinical and basic scientific research into the cause, prevention, detection, treatment and cure for Sjögren's.

The SSF is excited to now offer two distinctive one-year grants:

The SSF Pilot Research Award	\$25,000
The SSF High Impact Research Award	\$75,000

The deadline for the next grant cycle is:
February 1, 2019

Visit www.sjogrens.org to learn more!

"Clinical News" Continued from page 9 ▼

there were five cases (19%) positive for both biopsy and autoantibody, 18 cases (69%) positive for biopsy alone and three cases (12%) positive for autoantibody alone. No differences were found in lymphocyte focus scores, fibrosis rates and autoantibody positivity between the groups, though plasma cell focus was significantly higher in Sjögren's patients ($P=0.003$).

Citation

Kucuk U, Sarioglu S, Cetin P, Sari I & Birlık M. Histopathological differences between primary Sjögren's syndrome and Sjögren's syndrome accompanied by scleroderma. *Indian J Pathol Microbiol.* 2018 Jul-Sep;61(3):319-322. doi: 10.4103/IJPM.IJPM_416_17.

The Economic Burden of an Inadequate Response to Targeted Immunomodulators

Investigators have found that patients who do not respond to targeted immunomodulators (TIMs) are more likely to face a higher cost burden due to a higher utilization of health care resources, high all-cause medical costs, indirect costs and more lost days of work when compared to those who respond to the therapies.

Approximately one third of patients in this study were classified as TIM responders ($n=2,527$) with the remaining patients being classified as non-responders ($n=5,013$). Specifically, non-responders were found to have a significantly higher utilization of health care resources, including inpatient admissions (IRR=1.94), outpatient visits (IRR=1.19), emergency department visits (IRR=1.53) and number of prescriptions filled (IRR=1.09; all had a $P<0.001$). Non-responders also had significantly higher all-cause (\$12,868 vs. \$9,621, respectively) and rheumatoid arthritis (\$5,740 vs. \$4,495; both, $P<0.001$) related medical costs when compared to those classified as responders. Additionally, non-responders reported significantly more days of work lost compared with responders (22.1 vs. 16.7 days, respectively; IRR = 1.21; $P=0.007$) and higher indirect costs (\$3,548 vs. \$2,890; $P=0.002$).

Citation

Strand V, Tundia N, Song Y, Macaulay D & Fuldeore M. Economic burden of patients with inadequate response to targeted immunomodulators for rheumatoid arthritis. *J Manag Care Spec Pharm.* 2018 Apr;24(4):344-352. doi: 10.18553/jmcp.2018.24.4.344



Clinical News: Nephrology

RTA Presenting with Hypokalemic Paralysis Identified as Most Common Renal Manifestation of Sjögren's

In a recent study, renal involvement was found in 35 (50%) of Sjögren's patients, with 29 cases of renal tubular

acidosis (RTA) (25 complete and four incomplete) and 11 cases of urinary abnormalities. Compared to patients without RTA, patients with RTA were younger (34.9 ± 9 vs. 42 ± 11.3 , $p=0.006$), had fewer articular (34% vs. 78%, $P=0.001$) and ocular sicca symptoms (62% vs. 88%, $P=0.01$). Hypokalemic paralysis was also more common in patients with RTA. Biopsies found that TIN (9/17) and IgA nephropathy (3/17) were most common. No clinically significant changes in eGFR were found during follow-up. In all, 174 Sjögren's patients were initially screened, with 70 then undergoing renal function tests, urine examination, renal ultrasound, arterial blood gases, urine pH followed by urine acidification test and renal biopsy. At one year, 62 patients completed a follow-up.

Citation

Jain A, Srinivas BH, Emmanuel D, Jain VK, Parameshwaran S & Negi VS. Renal involvement in primary Sjögren's: a prospective cohort study. *Rheumatol Int.* 2018 Aug 23. doi: 10.1007/s00296-018-4118-x. [Epub ahead of print].



Clinical News: Neurology

Significant Association Between Sjögren's and Dementia Risk Identified

Using a population-based, retrospective-cohort study design, investigators have identified a significant association between Sjögren's and risk for dementia. Investigators looked at a variety of potential comorbidities, including Parkinson's disease (adjusted hazard ratio (aHR) = 2.98, 95% CI = 1.80–4.94), insomnia (aHR = 1.45, 95% CI = 1.14–1.85) and hypertension (aHR = 1.43, 95% CI = 1.19–1.71) and still found a significant association between Sjögren's and dementia. This data, from 2000-2012, was identified from the Longitudinal Health Insurance Database, which is maintained by the Taiwan National Health Research Institutes.

Citation

Chen HH, Perng WT, Chiou JY, Wang YH, Huang JY & Cheng-Chung J. Risk of dementia among patients with Sjögren's: a nationwide population-based cohort study in Taiwan. *Semin Arthritis Rheum* (2018). Doi:10.1016/j.semarthrit.2018.06.007

Impact of Disease Activity and Psychological Status on QoL in Sjögren's Patients

Results from a recent survey found a considerable decrease in the quality of life (QoL) of Sjögren's patients compared to healthy controls. A total of 185 Sjögren's patients and 168 healthy controls were included in the study, which found Sjögren's patients had lower scores in each domain of the SF-36 health survey. Using bivariate analy-

sis, age, pain, fatigue, disease activity, disease complication, anxiety/depression, oral disorders and impaired swallowing all correlated with QoL. Using linear regression, pain, fatigue, disease activity, impaired swallowing and anxiety/depression had the highest correlations with QoL.

Citation

Cui Y et al. The impact of disease activity and psychological status on quality of life for Chinese patients with primary Sjögren's syndrome. *Patient Prefer Adherence*. 2018 Aug 21;12:1513-1519. doi: 10.2147/PPA.S163417. eCollection 2018

Sjögren's and other Systemic Autoimmune Diseases Associated with Risk for OCD

After adjusting for demographic variables, patients with systemic autoimmune diseases (SADs) (n=63,135) were found to have an increased risk for the subsequent development of obsessive compulsive disorder (OCD) (HR: 1.85; 95% CI 1.41-2.43) when analyzed against a comparison cohort (n=315,825) identified from the Taiwan National Health Insurance Program Database. When looking at specific diseases, significant increases in the risk of OCD were seen in patients with systemic lupus erythematosus (SLE) (1.65, 1.07-2.54) dermatomyositis (3.25, 1.04-10.17), and Sjögren's (2.38, 1.53-3.72). Additional risk factors included age (50 years or less) as well as alcohol use disorder, liver cirrhosis and malignancies. Steroid use was identified as potentially being a protective factor against the development of OCD.

Citation

Wang LY, Chen SF, Chiang JH, Hsu Cy & Shen YC. Systemic autoimmune diseases are associated with an increased risk of obsessive-compulsive disorder: a nationwide population-based cohort study. *Soc Psychiatry Psychiatr Epidemiol*. 2018 Nov 7. doi: 10.1007/s00127-018-1622-y. [Epub ahead of print].



Clinical News: Gastroenterology

Differences in Pancreatic Elastase Identified Between Sjögren's and RA

Significant differences were found in pancreatic elastase, a marker for pancreatic exocrine functions, between Sjögren's patients, rheumatoid arthritis (RA) patients with Sjögren's, and healthy controls, though no differences were found between RA patients and the control group. Random fecal samples were taken from all participants, including RA patients (n=20), RA patients with Sjögren's (n=20), Sjögren's patients (n=20) and healthy controls (n=20), to identify whether RA contributes to pancreatic exocrine insufficiency. Fecal elastase levels were significantly higher in the RA group compared to the Sjögren's group, while no significant difference between the RA plus Sjögren's and Sjögren's groups were found.

Citation

Sisman P, Yucel E. Evaluation of pancreatic exocrine functions in rheumatoid arthritis. *Bratisl Lek Listy*. 2018;119(8):494-497. doi: 10.4149/BLL_2018_090.

Sjögren's and SLE Patients Have Similar Gut Microbiota; Differences Identified in Oral Microbiota

Researchers found that Sjögren's patients (n=39) and systemic lupus erythematosus (SLE) patients (n=30) shared similar differences in gut microbiota when compared to population controls (n=965). However, when comparing the oral microbiota, significant disease-specific differences were found between the two patient groups, which may be explained in part due to the dryness experienced by those with Sjögren's. Both patient groups were characterized by lower bacterial richness, lower Firmicutes/Bacteroidetes ratio and higher relative abundance of Bacteroides species in fecal samples compared to population controls. 16S ribosomal RNA gene sequencing was used on all fecal samples and buccal swab and oral washing samples were obtained from Sjögren's and SLE patients.

Citation

van der Meulen TA et al. Shared gut, but distinct oral microbiota composition in primary Sjögren's syndrome and systemic lupus erythematosus. *J Autoimmun*. 2018 Nov 9. pii: S0896-8411(18)30524-9. doi: 10.1016/j.jaut.2018.10.009. [Epub ahead of print].



Clinical News: Cardiovascular

Association Between Sjögren's, Arterial Stiffness and Subclinical Atherosclerosis

Sjögren's patients were found to have a significant increase in pulse wave velocity (PWV) (MD = 1.30 m/s; 95% CI 0.48-2.12; P value = 0.002; I2 = 85%) and higher intima-media thickness (IMT) (MD = 0.08 mm; 95% CI 0.04-0.11; P value < 0.01; I2 = 72%) when compared to controls. This study included 767 patients identified in eight observational studies evaluating the associations between Sjögren's, subclinical atherosclerosis and arterial stiffness, found in a search of the Medline and Embase databases.

Citation

Yong WC, Sanguaneko A & Upala S. Association between primary Sjögren's, arterial stiffness, and subclinical atherosclerosis: a systematic review and meta-analysis. *Clin Rheumatol*. 2018 Sep 3. doi: 10.1007/s10067-018-4265-1. [Epub ahead of print].

"Clinical News" Continued from page 11 ▼



Clinical News: Pulmonology

Treat-to-Target Strategy Found Effective for Treating PAH in Sjögren's Patients

Investigators have concluded that the treat-to-target approach is an effective strategy for treating Sjögren's patients with pulmonary arterial hypertension (PAH). This study used retrospective data from 62 Sjögren's patients with PAH confirmed by right heart catheterization collected from a single center between 2007 and 2017. The primary endpoint of this study was reaching the PAH treatment goals, which 32 of the involved Sjögren's patients achieved. The 1-, 3-, and 5- year cumulative rates of reaching the goals were 40.6%, 67.4%, and 73.9%, respectively. Predictive factors for successfully reaching the treatment goals included using immunosuppressants (HR 4.715, 95% CI 1.101-20.192, $P=0.037$) and right ventricular anterior-posterior diameter (RV-APD) >30 mm at baseline (HR 0.426, 95% CI 0.188-0.968, $P=0.042$).

Citation

Liu Z et al. Is it possible to apply the treat-to-target strategy in primary Sjögren's syndrome-associated pulmonary arterial hypertension? *Clin Rheumatol* (2018). doi.org/10.1007/s10067-018-4184-1.

ILD in Sjögren's: Sicca Versus Non-Sicca at Onset

A retrospective review of hospitalized patients between 2003 and 2012 identified a total of 1,341 patients, 102 of which were analyzed and recruited to study the differences between patients with sicca and non-sicca onset Sjögren's with interstitial lung disease (ILD). Investigators found that 51% of Sjögren's-ILD patients presented with non-sicca onset, but only 4% of these patients, compared to 34% of patients with sicca onset, were diagnosed with Sjögren's at onset ($P=0.000$).

It was also found that hyperglobulinemia (immunoglobulin G, 16 [12-21] vs. 21 [15-28] g/L, $P=0.032$), elevated rheumatoid factor (RF) titer (RF, 22 [20-171] vs. 104 [20-237] IU/mL, $P=0.048$) and anti-SSA and/or anti-SSB presence (anti-SSA and/or anti-SSB presence, 33% vs. 72%, $P=0.000$) were less prevalent in patients with non-sicca at onset compared to patients with sicca at onset. Additionally, for non-sicca onset patients, the typical interstitial pneumonia pattern was more common (20.0% vs. 14.3%), high-resolution computed tomography scores were higher (12 [88-15] vs. 8 [5-13], $P=0.070$), and predicted total lung capacity and forced

vital capacity were lower ($87 \pm 23\%$ vs. $97 \pm 20\%$, $P=0.050$; $88 \pm 28\%$ vs. $100 \pm 27\%$, $P=0.089$).

Citation

Gao H et al. Interstitial lung disease in non-sicca onset primary Sjögren's syndrome: a large-scale case-control study. *Int J Rheum Dis*. 2018 Jul;21(7):1423-1429. doi: 10.1111/1756-185X.13334.

Red Blood Cell Distribution as a Negative Prognostic Factor for Sjögren's-PAH

In Sjögren's patients with pulmonary arterial hypertension (PAH), investigators have found that a red blood cell distribution width (RDW) of greater than 15% was associated with a significantly worse overall survival compared to similar patients with RDW levels equal to or less than 15% (3-year survival rate 59.5 vs. 88.7% log-rank $P=0.015$). RDW levels were found to be higher in patients who decreased in follow-up (13.8 ± 2.6 vs $16.5 \pm 1.6\%$, $P=0.003$) and in those with higher New York Heart Association classifications (13.8 ± 1.8 vs $16.5 \pm 2.9\%$, $P<0.001$).

Citation

Hui M et al. Red blood cell distribution width as a potential predictor of survival of pulmonary arterial hypertension associated with primary Sjögren's syndrome: a retrospective cohort study. *Clin Rheumatol*. 2018 Sep 14. doi: 10.1007/s10067-018-4281-1. [Epub ahead of print].



Clinical News: Oral

Sjögren's Patients More Likely to be Without Teeth; Need Tooth Extraction

In a comparison of Sjögren's patients ($n=108$) and matched controls ($n=108$), investigators have found that significantly more Sjögren's patients (14.8%) were without teeth compared to the control group (1.9%) ($P=0.001$). Sjögren's patients were also found to have a 61% higher risk for having at least one tooth extraction as well as higher rates of extraction in each sextant ($P=0.001$ to $P=0.032$), with the highest rate being seen in the upper anterior sextant (3.4 times more frequent for Sjögren's patients). Though not a significant difference, more maxillary teeth (42) were extracted within the Sjögren's group than mandibular teeth (34).

Citation

Maarse F, Jan Jager DH, Forouzanfar T, Wolff J & Brand HS. Tooth loss in Sjögren's syndrome patients compared to age and gender matched controls. *Med Oral Patol Oral Cir Bucal*. 2018 Aug 27. pii: 22545. doi: 10.4317/medoral.22545. [Epub ahead of print]

Potential of Electrostimulation of the Lingual Nerve to Prompt Salivary Gland Regeneration

This study involved a double-blind, sham-controlled period of two months as well as an open-label period

of nine months and included three patients who had no collectable resting or stimulated saliva secretion. Once completed, patients developed the capacity to spit saliva both after electrostimulation as well as during free intervals without electrostimulation. Notably, symptoms of dry mouth severity and frequency improved. The authors state that these outcomes are likely due to a combined effect of an increase in secretory functional gland mass and regaining nervous control of the secretory elements and blood vessels.

Citation

Wolff A et al. Electrostimulation of the lingual nerve by an intraoral device may lead to salivary gland regeneration: A case series study. *Med Oral Patol Oral Cir Bucal*. 2018 Aug 27. pii: 22597. doi: 10.4317/medoral.22597. [Epub ahead of print].

An Analysis of Voice-Related Problems in Sjögren's

Voice handicap index (VHI) scores were found to be significantly higher in Sjögren's patients compared to healthy controls (median [interquartile range], 11 [3-30] vs. 5.5 [0- 15.75], $P=0.014$), however, no differences were found between the groups when comparing acoustic analysis aerodynamic studies and stroboscopic findings. Further analysis of Sjögren's patients found that jitter value was positively correlated with ESSDAI scores (spearman's $\rho = 0.29$, $P=0.048$) and patient global assessment ($\rho=0.3$, $P=0.04$) and high VHI scores were associated with lower quality of life as measured by EQ5D ($\rho=-0.493$, $P=0.0001$). Of note, patients with longer disease duration (≥ 40 months) showed a higher noise-to-harmonics ratio.

Citation

Kim SY et al. Do I sound dry? Comparative voice analysis of primary Sjögren's syndrome. *Clin Exp Rheumatol*. 2018 May-Jun;36 Suppl 112(3):130-136. Epub 2018 Aug 14.

ARFI May Be A Valuable Tool in Assisting With Clinical Diagnosis of Sjögren's

In a recent study, researchers sought to investigate the diagnostic value of Acoustic Radiation Force Impulse (ARFI) imaging in the assessment of salivary gland involvement in Sjögren's. Sjögren's patients ($n=25$) and healthy controls ($n=25$) were included and first underwent B-mode ultrasonography, which evaluated submandibular and parotid gland thickness and echostructures. Following this, ARFI imaging was used to collect 10 independent shear wave velocity (SWV) measurements for each gland, which were then averaged for a mean SWV value. After calculation, the cut-off of SWV values for submandibular glands and parotid glands were 1.98 m/s and 1.93 m/s, respectively.

Sjögren's patients were found to have significantly higher SWV values for both the parotid and submandibular glands compared to healthy controls ($P<0.001$).

No significant relationship was found between mean SWV values for parotid and submandibular gland symptom duration in Sjögren's patients (all $P>0.005$). Notably, the mean SWV values were higher in the parotid glands compared to the submandibular glands in Sjögren's patients ($P<0.001$).

Citation

Turnaoglu H, Kural R, Pamukcu M, Haberal KM & Uslu N. Diagnostic value of acoustic radiation force impulse imaging in the assessment of salivary gland involvement in primary Sjögren's syndrome. *Med Ultrason*. 2018 Aug 30;20(3):313-318. doi: 10.11152/mu-1397.

Taxa Associated with Sjögren's Identified in Buccal Mucosa

Investigators used 16S rRNA sequencing to determine the bacterial composition of the buccal mucosa in order to assess differences in Sjögren's patients ($n=37$) compared to non-Sjögren's sicca patients ($n=86$) and healthy controls ($n=24$). Upon analysis it was found that Sjögren's and non-Sjögren's sicca patients had higher ratios of Firmicutes/Proteobacterias. A total of 19 taxa were identified as being associated with Sjögren's patients compared to healthy controls, 12 of which correlated with salivary secretion. Only two taxa were identified as being associated with Sjögren's patients when compared to non-Sjögren's sicca patients. Of note, disease status and salivary secretion rate contributed nearly equally to the variation in bacterial composition between individuals, at 3.8% and 4.3%, respectively.

Citation

van der Meulen TA et al. Dysbiosis of the buccal mucosa microbiome in primary Sjögren's syndrome patients. *Rheumatology (Oxford)*. 2018 Jul 27. doi: 10.1093/rheumatology/key215. [Epub ahead of print].

SGSC Supplementation for the Restoration of Saliva Production in Sjögren's

Findings from this first of its kind study to characterize salivary gland stem cells (SGSCs) support that saliva production in Sjögren's patients is unlikely to be restored from disease-modifying antirheumatic drugs (DMARDs) alone and that treatment should be supplemented with SGSCs. Investigators used parotid gland biopsies from Sjögren's patients and compared them to those of healthy controls to assess self-renewal and regenerative potential. Upon comparison, the SGSCs from Sjögren's patient biopsies were found to have inferior regeneration capabilities compared to the controls and were both lower in number and less able to differentiate. Additionally, SGSCs from Sjögren's patient biopsies were more likely to be senescent compared to controls. RNA-Seq analysis, STELA analysis and immunohistochemical analysis were also used as part of the study.



Industry News

Oral Sjögren's Drug Fails to Produce Statistically Significant Results

A 30-person study investigating leniolisib (CDZ173) has produced acceptable, though not statistically significant, results when taken orally for 12 weeks by Sjögren's patients. Notably, the development of a rash, which is a known effect of P13K inhibitors, was much more common in the treatment group (11/20) versus those taking a placebo (1/10). Biomarker results suggest a strong and sustained target and pathway engagement, significant decrease in CXCL13, reduced frequency of circulating Follicular T helper-like cells and a trend towards decreasing autoantibody levels in the treatment group. The primary outcome of this study was a change in ESSPRI score at 12 weeks.

Citation

Dorner T et al. A randomized, double-blind study to assess the safety, tolerability and preliminary efficacy of leniolisib (CDZ173) in patients with primary Sjögren's. European League Against Rheumatism Annual Meeting 2018. Amsterdam, Netherlands.

MeiraGTx and NIDCR Agree to Global Rights for Sjögren's Treatment

MeiraGTx, a clinical stage gene therapy company, and the National Institute of Dental and Craniofacial Research (NIDCR), have agreed on terms for global rights to a gene therapy, adeno-associated virus vector mediated gene delivery of aquaporin-1, or AAV-AQP1, to treat Sjögren's and associated xerostomia and xerophthalmia.

Favorable Results for MC2-03 as DED Treatment

MC2 Therapeutic's, a clinical-stage dermatology and eye care company, has reported that MC2-03, an eye drop containing cyclosporin A and formulated using the company's proprietary PAD™ Technology, which was developed to enable improved penetration into the ocular tissues without the use of excipients, has shown clinical improvement in moderate to severe dry eye patients in a Phase II study. Treatment groups involved in the study consistently showed a higher proportion of corneal fluorescein staining improvement after six months when compared to controls.

Alcon Launches New Product to Treat All Types of DE

Alcon, a division of Novartis, has launched Systane Complete, a new first-line treatment for all major types of dry eye, including evaporative, aqueous-deficient and mixed dry eye. The new formula uses nano-droplet, intelligent moisture and lipid technology to enhance delivery of the active ingredient, propylene glycol, across the eye's surface to stabilize the tear film.

OLYMPIA Trial Launched for TearCare® System's iLid™ Device

Sight Sciences has launched the OLYMPIA trial, a pivotal study to explore the safety and efficacy of its TearCare® System's iLid™ device. The wearable therapeutic eyelid technology is designed to provide energy through the course of a specified period of time to liquefy meibum on the eye's surface. This randomized, controlled trial will include 200 patients and evaluate this new device against a daily regimen of warm compress therapy and eyelid massage. Patients will be followed for six months after treatment and will then be re-treated and followed for an additional six months. The study's primary endpoint is tear breakup time at one month.

Zessly® Receives EC Approval for Multiple Treatment Indications

The European Commission has approved Zessly®, an infliximab biosimilar developed by Sandoz with treatment indications for rheumatoid arthritis, Crohn's disease, psoriatic arthritis and more. Zessly® blocks the action of TNF-alpha in patients with certain autoimmune diseases where excess TNF-alpha may exacerbate or lead to onset of disease. This approval was based on a comprehensive data package, which confirms Zessly® matches the safety, efficacy and quality of the reference product.

"Clinical News" Continued from page 14 ▼

with fluorescein (75.6%) and anterior blepharitis (73.2%). This review found that private practitioners were more likely to use symptom questionnaires (34.3% vs. 0.00%; $P \leq 0.001$) and to describe anterior blepharitis (81.2% vs. 64.4%; $P \leq 0.001$) compared to academic settings. Optometric practices in academic settings were more likely to report tear breakup time (52.5% vs. 32.8%; $P \leq 0.001$) and tear meniscus height (28.8% vs. 12.5%; $P \leq 0.001$) compared to private practices. A total of 123 patients from six optometric practices in North American were included in this study.

Citation

Acs M et al. Customary practices in the monitoring of dry eye disease in Sjögren's. *J Optom.* 2018 Jul 14. pii: S1888-4296(18)30046-3. doi: 10.1016/j.optom.2018.05.001. [Epub ahead of print].

Reduction in Cys C and Other Endogenous Proteases May Enhance CTSS Activity in Sjögren's Tears

Investigators analyzed cathepsin S (CTSS) activity, cystatin C (Cys C), lactoferrin (LF) and secretory IgA (sIgA) levels in Sjögren's patients (n=33), rheumatoid arthritis patients (n=33), patients with other autoimmune

diseases (n=31), patients with non-autoimmune dry eye (n=35) and healthy controls (n=24) to determine if protease inhibition and Cys C levels are reduced in the tears of Sjögren's patients, which could lead to enhanced CTSS-driven degradation of tear proteins. Compared to other groups, tears of Sjögren's patients had significantly increased CTSS levels and significantly decreased levels of Cys C, LF and sIgA. Cys C and LF were found to have enhanced degradation in the tears of Sjögren's patients supplemented with recombinant CTSS, which was not seen in the tears from healthy controls. When combined, LF and CTSS improved discrimination of Sjögren's beyond CTSS in dry eye patients. The authors have stated that a reduction in Cys C and other endogenous proteases may enhance CTSS activity in the tears of Sjögren's patients. ■

Editor's note: The lead author, Dr. Maria Edman, is a previous recipient of an SSF grant.

Citation

Edman MC et al. Increased cathepsin S activity associated with decreased protease inhibitory capacity contributes to altered tear proteins in Sjögren's syndrome patients. *Sci Rep.* 2018 Jul 23;8(1):11044. doi: 10.1038/s41598-018-29411-9.

"Industry News" Continued from page 15 ▼

Encouraging Results for Tivanisiran as DE Treatment

Sylentis, a biotechnology company of PharmaMar, has shared promising results for SYL1001 (Tivanisiran) for the treatment of dry eye disease (DED). SYL1001 is a small synthetic double-stranded ribonucleic acid oligonucleotide that acts to inhibit the production of the transient receptor potential cation channel and is administered via preservative-free eye drop. Company representatives presented study results at the Association for Research in Vision and Ophthalmology's 2018 Annual Meeting that highlighted the improvement of ocular inflammatory parameters, tear quality and a reduction in ocular pain associated with DED.

Surface Pharmaceuticals, Inc. Announces Deal to Raise Proceeds for Clinical Development Programs

Surface Pharmaceuticals Inc, an affiliate of Imprimis Pharmaceuticals, Inc., has reached an agreement with an affiliate of Flying L Partners, to raise proceeds of approximately \$20 million of Series A preferred stock. Surface Pharmaceuticals intends to use these proceeds to continue to advance its clinical development program, which focuses on ocular surface disease, including the treatment of dry eye disease. The company has three drug candidates for which they are seeking FDA approval, SURF-100, SURF-200 and SURF-300.

Positive Results for Oyster Point's DE Treatment

Oyster Point's dry eye treatment, OC-02, a nicotinic acetylcholine receptor agonist delivered as a nasal spray, has met primary endpoints for both signs and symptoms in a Phase IIb clinical trial. Across all three dosage groups, OC-02 produced statistically significant changes in Schirmer score compared to controls. Using the Eye Dryness Scale, a significant reduction in symptoms was seen in the highest two dosage groups.

Aurinia Initiates Phase II Trial for Voclosporin as Treatment for DE

During the summer, Aurinia Pharmaceuticals, Inc., announced the beginning of a Phase II trial to evaluate voclosporin ophthalmic solution (VOS), compared to Restasis® (0.05% cyclosporine ophthalmic emulsion) for the treatment of dry eye syndrome. VOS is a nanomicellar formulation which enables high concentrations of voclosporin to be incorporated into a clear, aqueous and preservative-free solution for delivery to the ocular surface. The study will evaluate the tolerability of 0.2% VOS versus Restasis® at four weeks. Secondary endpoints in this study will include Ocular Surface Disease Index, System Assessment in Dry Eye, Individual Symptom Severity Assessments and Drop Discomfort Visual Analog Scale scores, Fluorescein Corneal Staining and Schirmer Test. ■

SSF In Action



SSF Leads Efforts to Update ICD-10 Codes

On September 11-12, 2018, in Baltimore, MD, the Centers for Medicare & Medicaid Services hosted the ICD-10 Coordination and Maintenance Committee Meeting: Public Forum to Discuss Proposed Changes to ICD-10-CM and ICD-10-PCS. On day two, Alan Baer, MD, presented on behalf of the Sjögren's Syndrome Foundation and the American College of Rheumatology, an overview of Sjögren's as well as the rationale for why changes to the ICD-10 code are being requested and needed. Dr. Baer's presentation was followed by a presentation by a representative from the Centers for Disease Control and Prevention on the specifics of the proposed tabular changes that were being requested.

A decision on the proposed changes is anticipated to be made by the end of 2018. A more in-depth article on this effort will be published in a future issue of *Sjögren's Quarterly*.

SSF Shows Support in Sign-on Letters

As part of the SSF's advocacy efforts, the Foundation has joined numerous other patient and professional organizations and signed-on to two letters of support.

The first, a letter addressed to HHS Secretary Azar, was related to step therapy and urged policy considerations to include patient protections. Specific requests included requirements for step therapy protocols to follow best practices or clinical practice guidelines, beginning treatment with the recognized standard of care, despite cost, and an expedient exception and appeals process, among others. More than 80 organizations signed-on to this letter.

The second, a letter addressed to Majority Leader Mitch McConnell and Minority Leader Charles Schumer, was on behalf of the Healthy Choices Coalition urging consideration for House Resolution 6199, the Restoring Access to Medication and Modernizing Health Savings Accounts Act of 2018. Passing this legislation would eliminate the need for Americans to obtain a prescription to purchase over-the-counter medicines, improving access to care within the U.S. healthcare system. ■

The SSF continues to attend and participate in numerous meetings and events held by a variety of stakeholders to help maximize our reach and ensure the Sjögren's community's voice continues to be heard. During the past few months, SSF staff have participated in events held by the National Health Council, U.S. Food and Drug Administration, National Institutes of Health, American Association for Dental Research and more. If there are groups or events that you believe the SSF could partner or be involved with, please share these suggestions by emailing sq@sjogrens.org.

SSF Outstanding Abstract Awards at ACR



Lauro Meneghel, MSc, PhD (center); Theresa Lawrence Ford, MD (left), Steven Taylor (right)



Saviana Gandolfo, MD (center); Theresa Lawrence Ford, MD (left), Steven Taylor (right)



Gaetane Nocturne, MD, PhD (center, accepting the award on behalf of Elodie Rivière, MD); Theresa Lawrence Ford, MD (left), Steven Taylor (right)

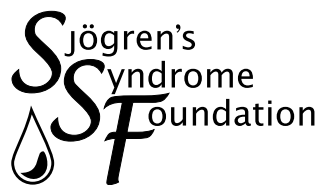
The Sjögren's Syndrome Foundation (SSF) was delighted to recognize three young investigators at this year's Outstanding Abstract Award presentation during the 2018 American College of Rheumatology's (ACR) Annual Meeting in Chicago, IL. Lauro Meneghel, MSc, PhD was announced as the winner and Saviana Gandolfo, MD and Elodie Rivière, MD, were announced as honorable mentions. All three were recognized for their exceptional work during the Sjögren's Study Group on Tuesday, October 23, 2018.

Dr. Lauro Meneghel, Karolinska University Hospital, Stockholm, Sweden, received the award for his abstract entitled, "Clinical Correlations and Expression Pattern of Autoimmunity Susceptibility Factor Diora-1 in Primary Sjögren's Syndrome." The findings from this study indicate a role for DIORA-1 in select B cell subsets and suggest that DIORA-1 potentially contributes to the inflammatory process and disease pathogenesis in Sjögren's through B cell involvement.

Dr. Saviana Gandolfo, University of Udine, Udine, Italy, received honorable mention for her abstract entitled, "Serum Levels of Thymic Stromal Lymphopoietin: A Possible Novel Biomarker in Primary Sjögren's Syndrome and Related Lymphoproliferation." This study found that thymic stromal lymphopoietin (TSLP) was significantly increased in Sjögren's, with further studies continuing, which involve Sjögren's cohorts belonging to the HarmonicSS consortium.

Dr. Elodie Rivière, Université Paris Sud - INSERM U1184, Le Kremlin-Bicêtre Cedex, France, received honorable mention for her abstract entitled, "RNA Sequencing Detection of Gene Dysregulation in B Cells Sorted from Salivary Gland Tissue and from Peripheral Blood Reveals New Pathways Involved in Primary Sjögren's Syndrome." Data from this study confirmed the B cell activation and differentiation through several markers, including CD40, CD22, CD48 and CD138 and highlighted the role of innate immunity with Toll-like receptor's and key pathways including IFN and JAK signaling. The precise understanding of these dysregulations should offer development of new targeted therapeutic perspectives for patients.

The SSF Outstanding Abstract Award is designed to recognize exceptional research efforts in the field of Sjögren's and encourage new or early stage investigators to continue their focus on Sjögren's throughout their career. The winning abstracts were selected by a distinguished panel of scientists from 54 eligible applicants and are available online at <http://www.sjogrens.org/home/research-programs/outstanding-abstract>. ■



Patient Education Sheet

Clinical Trials – Getting Involved

by Herbert S. Baraf, MD, FACP, MACR Clinical Professor of Medicine, George Washington University; and Managing Partner, Arthritis & Rheumatism Associates, PC, Wheaton, Maryland

Clinical trials provide the means for evaluating a new or existing treatment in patients to see if the treatment, usually a drug, is safe and effective and at what dose. Clinical trials are necessary before a therapy can be approved and offered on the market. Before enrolling in a clinical trial, always discuss participation with your doctor.

Why Consider Participating in a Clinical Trial? Patients participating in a trial will:

- Help ensure a new treatment is developed to control symptoms or overall outcome of their disease or disorder.
- Gain access to a promising treatment that may provide unique benefit or meet unmet need.
- Get access to care at no cost.
- Help other patients.
- Participate in helping to advance science/medicine.

Am I Eligible to Participate in a Clinical Trial?

- Clinical studies are performed according to a plan design called a protocol which is unique to each project.
- Protocols define eligibility criteria of participants who can be enrolled. These criteria relate to such factors as age, gender, duration of illness, prior treatments and other medications you might be taking, etc.
- Eligibility criteria fall into two categories:
 - Inclusion criteria which define the population of patients to be studied
 - Exclusion criteria which disqualify certain volunteers from participating due to age, other medical problems or other factors

Is it Safe to be in a Clinical Trial?

- Before participating, you will be provided with a document called an informed consent outlining risks and benefits and the study design (features of the protocol such as length of the study and number of visits). After reviewing that document, you might have questions, all of which should be answered.
- You have the right to withdraw from a study at any time and for any reason as is explained in all informed consent documents and by the personnel conducting the trial.
- The clinical trials program typically is monitored by an independent institutional review board that approves the study design and sites where the study is conducted.
- Most trials of new medications performed at multiple sites across the country are monitored on an ongoing basis by a data safety monitoring board.
- The FDA has oversight for the clinical trials process and periodically conducts audits at sites where trials are performed.
- Please see the Patient Education Sheet on "Understanding Clinical Trials" for more information on clinical trials. This sheet is available online at <http://www.sjogrens.org/home/about-sjogrens/brochures-and-fact-sheets>.
- Additional information and a list of specific trials currently available for enrollment can be viewed by visiting <https://info.sjogrens.org/clinical-trials>

For more information on Sjögren's, contact the Sjögren's Syndrome Foundation at:
10701 Parkridge Blvd., Suite 170, Reston, VA 20191 • 800-475-6473 • www.sjogrens.org • ssf@sjogrens.org.

Clinicians: Please make multiple copies of this Patient Education Sheet and distribute to your patients.

Sjögren's Quarterly

Sjögren's Syndrome Foundation Inc.
10701 Parkridge Blvd., Ste. 170
Reston, VA 20191

Learn more about Clinical Trials in Sjögren's!



The SSF has a section on its website devoted to clinical trials in Sjögren's. Visit <https://www.sjogrens.org/home/about-sjogrens/clinical-trials-whatsinvolved>

Links on this page take you to:

- An article by Theresa Lawrence Ford, MD, the SSF Medical and Scientific Advisory Board Chair and Chair of the SSF Clinical Trials Consortium
- The clinical trials 101 and getting involved fact sheets
- A list of clinical trials in Sjögren's that are currently recruiting Sjögren's patients

Let the SSF know if you are interested in incorporating clinical trials into your practice.

If so, we would like to learn more about you and your practice. We also often share potential clinical trial sites with our pharmaceutical members when those sites and patient populations fit the needs of a specific company and trial. Please contact us at sq@sjogrens.org if you currently engage in clinical trials or are interested in doing so.

