Phase 2 of the SSF Clinical Practice Guidelines for Sjögren’s Kicks Off!

Phase 2 of the Sjögren’s Syndrome Foundation (SSF) Clinical Practice Guidelines is well underway and will increase significantly the guidance offered on management and treatment of Sjögren’s and will expand the breadth and number of specialists involved who have not traditionally been involved with Sjögren’s and the SSF. SSF CEO Steven Taylor notes, “This second phase of the Foundation’s Clinical Practice Guidelines not only continues our engagement in an area that is critical for patients and healthcare professionals, but the initiative as a whole marks an incredibly ambitious undertaking and commitment on the part of the SSF and its Board of Directors. The Foundation decided to embark on this initiative because we believe that offering clinicians the best management and treatment tools for Sjögren’s patients is critical to excellent and consistent care.”

Phase 1 Paving the Way

Phase 1 wrapped up this past spring with the publication of the first guidelines under rheumatology and systemic management which addressed three topics: Fatigue, DMARDs and Inflammatory Musculoskeletal Pain, and Use of Biologics. This latest publication followed on the heel of three additional journal articles covering a summary of the rheumatology, ocular and oral guidelines; oral guidelines on caries prevention; and ocular guidelines that covered all aspects of ocular involvement and based treatment on four severity levels with and without meibomian gland disease. In addition to these publications, posters, presentations and one-page summaries were used to convey this information to practitioners both at professional meetings as well as through the SSF website.

TFOS DEWS II: Dry Eye Redefined!

by Jennifer P. Craig, PhD, MCOptom, FAAO, FBCLA, FCCLSA
Associate Professor, Department of Ophthalmology, The University of Auckland, New Zealand

A decade has passed since the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) published their report concerning this common, debilitating condition. Since that time, the volume of published literature on the topic of dry eye and ocular surface disease has almost doubled, thanks to the forethought and passion of TFOS in encouraging research collaboration and academic conversation. We have witnessed a rise to the challenge by scientists, clinicians and industry, in deepening our understanding and seeking solutions to
Phase 2 Expands Available Guidelines

Phase 2 will expand the number of topic areas covered by SSF Clinical Practice Guidelines in Sjögren’s from three in Phase 1 to a cumulative total of eight topics under systemic disease and from one to four topics under oral manifestations; add cross-cutting recommendations that span rheumatology, oral and ocular medicine; and will update all areas of ocular management and treatment.

Under the leadership of Steven E. Carsons, MD (Chief, Rheumatology, Allergy, Rheumatology, NYU Winthrop University Hospital), Phase 2 builds on the initial direction of Frederick Vivino, MD (Chief, Rheumatology, Penn Presbyterian Medical Center; Director, Penn Sjögren’s Syndrome Center; and Professor of Clinical Medicine, Philadelphia), who led the first-ever guidelines in Sjögren’s on behalf of the Foundation. Phase 2 topics are delineated below.

Systemic Manifestations of Sjögren’s

The Rheumatology/Systemic Disease section is chaired by Nancy L. Carteron, MD of the University of California, San Francisco and co-chaired by R. Hal Scofield, MD of the Oklahoma Medical Research Foundation, University of Oklahoma Health Sciences Center, and Department of Veterans Affairs Medical Center. Topic areas covered in Phase 2 are:

- pulmonary
- central nervous system
- peripheral nervous system
- lymphoma and other blood cancers
- vasculitis

During Phase 1, the Rheumatology/Systemic Working Group considered topics recommended by all stakeholders via SSF surveys and, after identifying 97 potential topics, narrowed the number to 16 key areas. Working Group members then provided scores from 1-5 for each of these areas, and nine topics received a score of >4.0. Final selections for Phase 1 were based on rankings as well as feasibility.

Phase 2 topics were selected based on these rankings. Because of the complexity of these topics, multiple specialists have been invited to participate and provide critical experience and expertise.

The Pulmonary Topic Review Group is led by R. Hal Scofield, MD (Rheumatology) and Augustine Lee, MD (Pulmonology, Mayo Clinic, Jacksonville, Florida). This group is made up of rheumatologists and pulmonologists and addresses areas of potential pulmonary complications in Sjögren’s including:

- interstitial lung disease
- obstructive lung disease
- bronchiolitis and bronchiectasis
- pleural disease
- diaphragm disorder
- cystic lung disease
- pulmonary hypertension
- thromboembolic disease
- alveolar hemorrhage
- anti-phospholipid antibody syndrome
- non-tuberculous mycobacterium, and
- neoplasms

The Central Nervous System Topic Review Group, led by Steven Mandel, MD (Neurology, Hofstra Northwell School of Medicine and Lenox Hill Hospital, New York) and Frederick Vivino, MD (Rheumatology), is made up of specialists in rheumatology, neurology, neuro-ophthalmology, neuropsychology, psychiatry, and neurology and sleep. Areas to be covered include:

- seizures
- stroke
- vasculitis and vasculopathy

Continued from page 1

Continued on page 4
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Shiboski, DDS, MPH, PhD
(University of California San Francisco School of Dentistry, San Francisco, California). After covering Caries Prevention during Phase 1, this next phase of oral guidelines will address:

- Caries Management and Restoration
- Mucosal Management and Symptom Relief
- Use of Secretagogues

The Caries Management and Restoration Topic Review Group will be led by Mabi Singh (Tufts University School of Medicine, Boston, Massachusetts), the Mucosal Management and Symptom Relief TRG led by Ibtisam Al-Hashimi, BDS, MS, PhD (The University of Texas Southwestern Medical Center, Dallas, Texas); and the Use of Secretagogues TRG by Athena Papas (Tufts University).

Ocular Manifestations of Sjögren’s
SSF Clinical Practice Guidelines for Ocular Manifestations of Sjögren’s will be chaired by Peter Donshik, MD (University of Connecticut Health Center Division of Ophthalmology, Farmington, Connecticut) and co-chaired by Michael Goldstein, MD (Tufts University School of Medicine, Boston, Massachusetts). This group will update the ocular guidelines published under Phase 1 and build on the findings of the 2017 TFOS DEWS II Report (see page 1 article in this issue by Jennifer Craig, MD).

Additional Topic Bridging Rheumatology, Oral and Ocular Medicine
An additional topic – Parotid and Lacrimal Gland Swelling – cuts across all three major specialties (rheumatology, oral and ocular medicine). This Topic Review Group will be comprised of specialists in rheumatology, oral medicine, ophthalmology, and oncology. Ava J. Wu, DDS (Sjögren’s Syndrome Clinic, University of California San Francisco) will lead this Topic Review Group.

Methods
After consulting on the best guidelines methodology with professional organizations such as the American College of Rheumatology and the American Dental...
Association as well as guidelines consultants from the American Society of Clinical Oncology (Patricia Hurley, MSc, HRM) and the GRADE methodology system for providing a systemic approach to rating quality of evidence and strength of recommendations (Holger Schünemann, MD, PhD, MSc, FRCP, McMaster University, Ontario, Canada), the SSF devised a guidelines development process that emphasized rigorosity and transparency. This process informed all aspects of guideline development, which includes drafting clinical questions, pre-selecting parameters for acceptable studies, extracting data from those studies, and using a Delphi-type approach to gain consensus for recommendations. The latter consisted of Consensus Expert Panels made up of a minimum of 30 professional experts and patients to review and vote on recommendations and provide input until at least 75% consensus was reached and all input was considered by those drafting the recommendations. The same process is being followed for Phase 2.

Phase 2 is consulting and working closely with the guidelines staffs of the American Academy of Neurology for the CNS and PNS Topic Review Groups and with the guidelines staff of the American Society of Clinical Oncology for the Lymphoma and Other Blood Cancer Topic Review Group. The Sjögren’s Syndrome Foundation aims to reach out to other specialists via their professional organizations in the hope of obtaining broader acceptance and distribution of the guidelines and increasing awareness among these different specialty groups.

**Calling for Members of the Consensus Expert Panels**

If you have an interest in serving on one or more of the Consensus Expert Panels (CEPs) for the next sets of Recommendations for Management and Treatment of the following areas in Sjögren’s – Pulmonary, Central and Peripheral Nervous System manifestations, Lymphoma and Other Blood Cancers, and Vasculitis – please let us know by emailing sq@sjogrens.org and providing your name, degree(s), institution or private practice name and location, and area of expertise. We will need health care professionals (MD, DMD, DDS, Physician’s Assistants, nurses and pharmacists) with expertise in rheumatology, pulmonology, neurology, oncology, dentistry, ENT, oral medicine, optometry and ophthalmology. Patients who also are health care professionals are encouraged to contact us about participating on the CEP.

The Sjögren’s Syndrome Foundation wishes to thank all of those who served on one or more Consensus Expert Panels for Phase 1. Please see the lists in this issue of the Sjögren’s Quarterly of those who volunteered their expertise and time to make Phase 1 possible.

**References**


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**Phase 1 of SSF Sjögren’s Clinical Practice Guidelines (CPG) Fast Facts**

- 56 Recommendations were issued for oral, ocular and rheumatology/systemic management and treatment aspects for Sjögren’s patients
- 172 volunteers were involved in the CPG initiative
- 8 patients participated on the Expert Consensus Panels that voted on the Recommendations
- 42 experts led the effort for oral, ocular and rheumatology/systemic guidelines
- 129 experts participated in the Expert Consensus Panels that reviewed and voted on Oral and Rheumatology Recommendations
- 6 posters were presented at professional meetings on the guidelines
- 2,153 abstracts were reviewed for oral and rheumatology guidelines

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**SSF16126.05**
The SSF Thanks all Consensus Expert Panel Members for the Rheumatology/Systemic Guidelines Phase 1

The Sjögren’s Syndrome Foundation wishes to thank the many experts who helped make Phase I of the Rheumatology/Systemic Clinical Practice Guidelines possible by serving on the Consensus Expert Panel that provided the Delphi-type process for ascertaining feedback on the proposed Recommendations and the Clinical Rationale on which they were based. These experts volunteered their time and knowledge.

The following served on at least one Consensus Expert Panel for the Recommendations for Rheumatology/Systemic Guidelines for Fatigue, Inflammatory Musculoskeletal Pain, and the use of Biologics in Sjögren’s. Many members served on all topic panels. Anyone serving on a Topic Review Group for a specific recommendation did not serve on the Consensus Expert Panel for that recommendation.

**Rheumatology**
Senada Arabelovic, DO
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Julius Birnbaum, MD, MHS
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Nancy Carteron, MD, FACR
Harjinder Chowdhary, MD, FACR
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Theresa Lawrence Ford, MD, FACR
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Robert Fox, MD, PhD, FACP, FACR
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Gary Foulks, MD, FACS
Michael Lemp, MD
J. Daniel Nelson, MD
Kelly Nichols, OD, MPH, PhD

**Other Professional Health Specialists**
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Fred Friedberg, PhD
Heidi Kukla, RN, BSN, CCRN, CNIII
Donald Lewis MacKeen, BS Pharm, MS Pharm, PhD
Steven Mandel, MD
Joan Manny, RN*
Lynn Petruzzi, RN, MSN*
Sarah Schafer, MD*
Nancy Schoofs, RN, PhD*

* Sjögren’s patient

** Oral and Ocular members participated in the Biological Therapy-Sicca Symptoms guidelines only, with the exception of the first name under Oral experts.
The SSF Thanks all Consensus Expert Panel Members for the Consensus Expert Panel for Oral Guidelines Phase 1

The Sjögren’s Syndrome Foundation wishes to thank the many experts who helped make Phase I of the Oral Clinical Practice Guidelines possible by serving on the Consensus Expert Panel that provided the Delphi-type process for ascertaining feedback on the proposed Recommendations and the Clinical Rationale on which they were based. These experts volunteered extensively of their time and knowledge.

The following served on at least one Consensus Expert Panel for the Recommendations for Caries Prevention in Sjögren’s. Many members served on all topic panels. Anyone serving on a TRG for a specific recommendation did not serve on the Consensus Expert Panel for that recommendation.

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Ava J. Wu, DDS
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Domenick Zero, DDS, MS

* Sjögren’s patient

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British Society for Rheumatology Publishes Guidelines

Guidelines for managing adults with Sjögren’s have just been published on behalf of the British Society for Rheumatology Standards, Guideline and Audit Working Group. Areas covered include treatment of sicca manifestations, salivary gland enlargement, non-pharmacological interventions for systemic disease, and immunomodulation for systemic disease. The SSF applauds this group for providing an additional management tool that will help healthcare professionals and patients.


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“TFOS DEWS II” Continued from page 1 ▼

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The Sjögren’s Syndrome Foundation is excited to announce that the 2017-2018 research grant recipients have been selected. For 2017, the research review committee sought grants which focused on biomarker development for Sjögren’s and how to monitor disease risk and prognosis, though all high-caliber, innovative projects were considered.

After careful consideration of this year’s outstanding pool of applications, the research review committee awarded three new research grants and renewed three excellent research grants from the 2016-2017 awardees.

2017-2018 Research Award Recipients:

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, Maryland

Research Project
Epithelial Cells and Innate Lymphoid Cells Collaborative Role in the Pathogenesis of Primary Sjögren’s Syndrome

Abstract
The immunopathogenesis of Sjögren’s and the active role of the glandular epithelium is not entirely understood thus limiting therapeutic approaches. We found for the first time, in human and mouse salivary glands, that ductal epithelial cells overexpress the prostanoid receptor CRTH2 during Sjögren’s autoimmunity. Importantly, CRTH2 blockade is a promising therapeutic strategy in asthma. Also, we found that innate lymphoid cells (ILCs), a subset of epithelium-associated leukocytes, infiltrate salivary glands and show pro-inflammatory properties in Sjögren’s and its murine model (autoimmune regulator knock-out). We hypothesize that ductal epithelial cell activation via CRTH2 ligation leads to ILC activation and recruitment, thus perpetuating the inflammatory response. This translational project aims to investigate the pathogenic features of salivary epithelial cells and ILCs on Sjögren’s in humans and murine models and might potentially lead to new therapeutic/diagnostic approaches.

SSF Research Grant Reviewers concluded that “understanding the epithelial cell/immune cell interface is highly important in further understanding Sjögren’s pathogenesis. [There is a] high probability that significant findings will come from this project.”

Danielle Marie Robertson, BS, OD, PhD

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

Research Project
Comparative Structural and Molecular Analysis of Tear and Salivary Derived Exosomes in Sjögren’s Syndrome

Abstract
The major problem facing Sjögren’s patients and clinicians today remains the absence of effective biomarkers to allow for early detection and treatment of the disease. Based upon available data, we propose to test a hypothesis that saliva and tear derived from exosomes will contain biomarkers unique to patients with primary Sjögren’s. We will test this hypothesis by characterizing the ultrastructural biology and molecular signature of saliva and tear derived exosomes from women with primary SS compared to age-matched healthy controls using cryo-electron microscopy and next generation RNA-sequencing. The identification and characterization of the exosomal structure and molecular profile is the first step in the identification of novel, early biomarkers for Sjögren’s. Upon review, an SSF Research Grant Reviewer felt that “this study has the potential of elucidating new biomarkers for Sjögren’s,” which could prove a very important advancement to the field. Additionally, this project involves a “newly formed Center of Excellence for Sjögren’s Clinical Care and Research that is multi-disciplinary and involves an excellent team and infrastructure.”

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address the conundrum where patients present with signs but no symptoms, or with symptoms but few clinical signs. Neuropathic pain is one such subset of patients with symptoms vastly out of proportion to clinical signs and is an indication for non-dry eye therapy. This form of sensitisation is explained in more detail in the Pain and Sensation report.

The Epidemiology, the Sex, Gender, and Hormones, and Iatrogenic Dry Eye reports describe modifiable and non-modifiable risk factors for dry eye disease, helping inform the most appropriate education and patient management. Consistent non-modifiable risk factors identified include increasing age, female sex, Asian ethnicity, certain systemic diseases, and meibomian gland dysfunction, while modifiable risks include hormone imbalance, environmental conditions such as relative humidity and computer use, and iatrogenic causes relating to medication use and surgery.

The reports on Pathophysiology and Tear Film outline the ocular surface tissue changes and alterations in tear film components that can occur in response to dry eye disease. Tear hyperosmolarity secondary to evaporative tear loss is considered the main proponent, setting off a cascade of events that leads to what has been termed the ‘vicious circle of dry eye disease’ - a symptomatic and self-propagating cycle of instability, hyperosmolarity, inflammation and cellular damage. Aqueous deficient dry eye and evaporative dry eye continue to be identified as the main dry eye disease subtypes, with the evaporative form more common of the two, although rarely occurring in isolation. There is considerable overlap recognised to exist between these two subtypes in many individuals.

The Diagnostic Methodology report recognises that global consistency in diagnostic criteria for dry eye disease has the potential to enhance our knowledge of dry eye prevalence and facilitate clinical trial outcome comparisons across the world. The latest diagnostic recommendations encourage exclusion of non-dry eye conditions and comorbidities as a first step. This can be achieved with a series of triaging questions. The report then recommends application of a specific series of tests of symptoms and signs in order to diagnose a dry eye.

The TFOS DEWS II report explains that dry eye is diagnosed when a patient demonstrates:

- a positive test score on a validated symptoms questionnaire (scoring ≥ 6 on the DEQ-5 or ≥13 on the OSDI), AND

- shows loss of tear film and ocular surface homeostasis, with a positive result on one or more of the following clinical tests:
  - a non-invasive tear break up time of < 10 seconds (note that fluorescein should be used only if a non-invasive test cannot be applied)
  - hyperosmolarity of ≥ 308 mOsm/L in either the right or the left eye, or an interocular difference exceeding 8 mOsm/L
  - ocular surface staining with fluorescein or lissamine green of > 5 spots on the cornea, or > 9 spots on the conjunctiva, or alternatively ≥ 2mm length and ≥ 25% lid margin width staining of the lid wiper zone

After a diagnosis is confirmed, further testing is necessary to evaluate the relative contributions of aqueous deficient and evaporative subtypes to the clinical picture and to point to the best management strategy. A predominantly aqueous deficient dry eye can be identified through tests of tear volume such as tear meniscus height measurement whereas a predominantly evaporative dry eye may be confirmed with tests of meibomian gland function such as expressibility and tear lipid layer quality.

The aim of dry eye disease management is to restore tear film homeostasis. This is most commonly achieved with longer-term therapies that aim to restore and maintain homeostasis but might also involve shorter-term treatments that are used to break the vicious cycle of dry eye disease. The Management and Therapy report presents staged treatment options as Steps 1 through 4. Therapy is expected to progress to the next step if resolution fails to be achieved at the lower level, but the practitioner is encouraged to use the dry eye subtype and severity to inform the most appropriate starting point.

TFOS DEWS II has drawn attention to a world of possibilities that lie ahead for eye care practitioners and the dry eye patients under their care. Our knowledge has been updated and revised guidelines have been provided to improve the clinical diagnosis and management of dry eye disease. The report makes recommendations for future research, and the Clinical Trials report explains best practice in designing and conducting randomised controlled trials, which can help inform the field in reaching its goals of reduced suffering at the hands of dry eye disease. It’s a remarkable privilege being part of this rapidly progressing field. I, for one, am excited to see what the next decade brings for dry eye, and I invite you to join with me in taking the plunge and meeting the challenge head on!!
Understanding the Complexity of Lymphoma in Sjögren’s Syndrome: A New Family of Receptors is identified as a Risk Factor


Abstract

Background

P2X7 receptor (P2X7R), trigger of acute inflammatory responses via the NLRP3 inflammasome, is hyperfunctioning in patients with Sjögren’s syndrome (SS), where it stimulates IL-18 production. Some patients with SS develop a mucosa-associated lymphoid tissue non-Hodgkin’s lymphoma (MALT-NHL).

Objectives

To prospectively evaluate the involvement and the putative prognostic role of this inflammatory pathway in the development of MALT-NHL.

Methods

A total of 147 women with SS have been prospectively followed for a mean of 52 months, relating the expression and function of the P2X7R-inflammasome axis in salivary glands and circulating lymphomonocytes to the prognosis and the degree of the disease.

Results

At baseline, gene expression of P2X7R and of the inflammasome components NLRP3, caspase-1 and IL-18 increased according to the presence of germinative centres and was higher in autoantibody-positive individuals and strongly higher in those developing a MALT-NHL over the follow-up. Glandular expression of IL-18 was threefold higher in MALT-NHL than in controls or in the other patients with SS. P2X7R did not colocalize with generic markers of inflammatory infiltrate, like CD20, being selectively expressed by epithelial cells. P2X4R, sharing functional characteristics with P2X7R, did not differ in SS and controls. The increased P2X7R gene and protein expression was tissue specific, no difference being observed in peripheral lymphomonocytes between SS with MALT-NHL and SS not developing MALT-NHL.

Conclusion

We propose the P2X7R-inflammasome axis as a novel potential pathway involved in both SS exocrinopathy and lymphomagenesis, reinforcing the hypothesis of a key role of IL-18, via its increased P2X7R-mediated production, in the pathogenesis of lymphoproliferative malignancies, and opening novel opportunities for the early diagnosis of lymphoproliferative complications and the development of potential targeted therapies.

Commentary

Baldini et al have recently reported that activation of a novel family of receptors is associated with non-Hodgkins lymphoma in Sjögren’s patients. Lymphoma is a particular concern in Sjögren’s, since it is 20-40 times more common in Sjögren’s than in other autoimmune diseases including systemic lupus erythematos (SLE) or rheumatoid arthritis (RA).

At present, it is not known if this family of receptors (called purinogenic P2Y7R) is causally related to lymphoma in Sjögren’s. Further studies will help us determine if measurements of this family will provide diagnostic information or targets for therapy beyond other factors already reported to be associated with lymphoma in Sjögren’s (Table 1).

This intriguing discovery demonstrates that a new pathway is now open for research. The receptor family is called “purinogenic,” since it releases ATP (adenosine tri-phosphate) and adenosine is a member of a class of molecules called purines. ATP, in addition to its important role as an energy source for cell metabolism, regulates certain metabolic pathways called gated channels in a variety of cell types including lymphocytes.
Abstract

The purpose of this research is to study the feasibility and efficacy of Fecal Microbiota Transplant (FMT) in Sjögren’s patients. Given the immune destruction of exocrine glands seen in Sjögren’s, severe immune modulators have been evaluated as treatments but none have consistently improved gland function and/or clinical metrics of disease. Individuals with Sjögren’s have been found to have gut dysbiosis, or a less diverse gut microbiome with a greater abundance of pathologic organisms and a lower abundance of healthy ones. In fact, the severity of ocular and systemic disease in Sjögren’s inversely correlated with microbial diversity. Furthermore, mice that spontaneously develop Sjögren’s and dry eye were also found to have gut dysbiosis. Dry eye in these mice worsened when given antibiotics and improved when fed feces from a healthy animal. This brings into question whether Fecal Microbiota Transplant (FMT) can improve the dry eye phenotype in patients with SS.

An SSF Research Grant Reviewer believes that Dr. Galor’s project “has the potential to revolutionize the treatment of Sjögren’s.”

Renewed 2016-2017 Research Awards

Stergios Katsiougianis, PhD
Assistant Project Scientist, Center for Oral/Head & Neck Oncology Research, UCLA School of Dentistry
Research Project
System Analysis of Mouse Models for Sjögren’s Syndrome Pathogenesis

Description

This study proposes a new method to produce eye drops that allow proteins to remain at the surface of the eye for up to 16 hours and consequently have time to act. This versatile technology will allow using therapeutic proteins to address other eye-related problems in Sjögren’s, such as corneal haze, pain, and insufficient secretion of tears.

Xaralabos Varelas, PhD
Assistant Professor, Department of Biochemistry, Boston University School of Medicine
Research Project
Defining Epithelial Cues Contributing to Sjögren’s Syndrome

Description

This study aims to define the molecular events accompanying the structural changes that occur in the organs of Sjögren’s patients, and to test whether promoting such defects in animal models will lead to similar disease symptoms. This will help define biomarkers of disease progression and offer new targets for therapeutic development.

For a full description of renewed research awards, please view the abstracts on the SSF website at www.sjogrens.org/home/research-programs/research-grants/current-recipients or see the Sjögren’s Quarterly, Volume 11, Issue 4 – Fall 2016.
Clinical News

Rheumatology

The ACR Issues Guidelines for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

The American College of Rheumatology (ACR) has recently developed guidelines and recommendations to provide direction for clinicians and patients for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP). Recommendations include treating GIOP with calcium and vitamin D for adults with low fracture risk and adding an oral bisphosphonate to the treatment regime for adults who have a moderate-to-high fracture risk. Additionally, for adults whom an oral bisphosphonate is not appropriate, or who finish the oral bisphosphonate course but still need additional treatment, it is recommended to switch to another anti-fracture medication. The ACR has also issued recommendations for special populations, such as children and organ transplant recipients. Because of the relative lack of evidence related to the benefits and harms of glucocorticoid use, recommendations should be considered conditional.

Citation

Associated Risk for Hematologic and Other Cancers in Patients With Sjögren’s

A team of Spanish researchers have conducted a study to characterize the risk of a cohort of patients with primary Sjögren’s Syndrome (pSS). Using Spanish mortality data, 1,300 patients fulfilling the criteria for a Sjögren’s diagnosis were identified and followed to help determine the associated cancer risk. Of the 1,300 patients analyzed, 127 developed some form of cancer, the most common of which were B cell mucosa-associated lymphoid tissue (MALT) lymphomas (n=27), other B cell lymphomas (n=19), breast cancer (n=14), colorectal cancer (n=9) and myeloid neoplasia / leukemia (n = 8). Compared to the general Spanish population, patients with Sjögren’s were eleven times more likely to develop a hematologic cancer. Sjögren’s was also associated with a higher risk of thyroid, oral cavity and stomach cancers. The authors recommend that patients with pSS should be closely monitored for hematologic and other associated cancers.

Citation

Study Finds Sjögren’s to be a Risk Factor for Acute Pancreatitis

Chinese researchers have published their findings from a population-based retrospective cohort study investigating the risk of acute pancreatitis in patients with primary Sjögren’s Syndrome (pSS). Using Taiwan’s National Health Insurance database, 9,468 patients with pSS were identified and compared to a control group made up of 37,872 age- and sex-matched controls from the general population. During the follow-up period, researchers found that patients with pSS had both a significantly higher rate of pancreatitis (0.46% vs. 0.28%) and incidence rate (100/100,000 vs. 58.6/100,000) compared to the control group. A Kaplan-Meier analysis also found a significantly higher cumulative incidence of acute pancreatitis in patients with pSS than in the controls. Additionally, the hazard ratio was 1.48 times greater in patients with pSS than in the controls, suggesting that pSS is an independent risk factor for acute pancreatitis.

Citation
The paper describes the “over-activation” of a part of the immune system called the “innate” system. The innate immune system is the first line of defense against viral, bacterial or parasitic pathogens, as well as remnants of dying cells.

Table 1. Reported Risk Factors for Lymphoma in Sjögren’s Patients

- Follicular dendritic cells and particular types of T cells in the minor salivary gland biopsy
- Activation of particular families of the innate immune system that lead to liberation of interferon, B cell activation factors, and tumor necrosis factor
- Alteration in DNA called “translocation” such as MALT lymphoma with t(14;18)(q32;q21)
- Expression of a class of regulatory RNA molecules called microRNAs (miRNAs)
- CD10 and Bcl10 expression in diffuse large B cell lymphoma: CD10 is a marker of improved prognosis
- Purinogenic Receptor P2Y7R that liberates ATP and thus governs certain cellular metabolic pathways

The innate system contains at least 15 different families of receptors that recognize different commonly expressed molecular structures on bacteria, viruses, or debris released by dying cells.

Several of these families have previously been associated with lymphoma (Table 1), but the paper adds another family of receptors to the list of potential candidates.

It is likely that lymphoma results from a combination of activation of several of these families as well as molecular “faults” in controlling the family members after activation.

The role of the innate system in autoimmune diseases has been known for over 30 years, and most attention has focused on the pathways leading to release of factors by:

- T cells of interferon,
- B cell activating factor (BAFF), and
- Tumor necrosis factor (TNF).

Of interest in this paper, the distribution of the purinogenic receptor and its related lymphocyte hormone (IL-18) are located in the monocytes adjacent to the ductal gland cells, rather than in the T cells or B cells. This suggests that the ducts may be contributing to the stimulation of the B-lymphocytes. In response to inappropriate and continued stimulation, the B cell makes a molecular error that leads to it becoming a lymphoma.

The factors that turn an “autoimmune lymphocyte” into a lymphoma may include DNA mutations and regulatory (micro) RNA species (Table 1). Also, the failure of other regulatory cells that normally “turn off” stimulated B cells.

It is easy to drown in the molecular biology of this ever-increasing number of “chips” in the human immune system “computer.”

Take-home Points

Patients with Sjögren’s Syndrome have a significantly increased frequency of non-Hodgkin’s lymphoma, particularly a form called “mucosal associated lymphoid tumor” (MALT).

These MALT lymphomas are due to B cells, and have an unusually high distribution in the parotid and submandibular lymph nodes-- the same salivary glands that are involved in symptoms of dryness.

Increased frequency in lymphoma (both MALT and a related lymphoma “diffuse large cell lymphoma” (DLCL) distinguish SS from other autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or scleroderma (SSc).

Sjögren’s sits at the interface of autoimmunity and lympho-proliferation. This tendency of “aggressive lymphocytes” gives rise to the characteristic focal infiltration of the salivary glands seen on gland biopsy.

Lymphocytic infiltrates in other tissues such as certain pulmonary manifestations (lymphocytic interstitial pneumonitis) and renal interstitial nephritis-- result from “aggressive” lymphocytes, although they do not fulfill criteria as lymphoma.

This lymphocyte-aggressive behavior makes it important to distinguish Sjögren’s from SLE or RA in terms of pathogenesis as well as therapeutic needs.

In Summary

Baldini et al have found an association with a member of the innate immune system (receptor family P2X7R) and subsequent development of lymphoma.

As a result of activating this receptor, a series of events that involve production of ATP (an important source of energy for cell division) and production of a lymphocyte hormone (called IL-18) known to facilitate cell replication is liberated.

Although this new finding may provide a clue to pathogenesis, it is far too early to assess its clinical significance or to use it as a marker for early aggressive therapy.
Aspirin as a Novel Dental Therapy

Through combining genomics and bioinformatics, researchers from Queen’s University Belfast, Belfast, Ireland, have found that aspirin may stimulate existing stem cells which aid in the regeneration of damaged teeth. Researchers found that low-dose aspirin led to a significant increase in mineralization and expression of dentine-forming genes. Next, the research team is planning to develop a drug delivery system to test the efficacy of aspirin to promote tooth repair during future clinical trials.

Citation

This research was presented at the British Society for Oral and Dental Research Annual Conference and has not been published at the time the SQ was published.

L-Arginine use for the Prevention of Dental Caries

A recent study sought to investigate the effect of L-arginine on the growth and biofilm of four types of oral bacteria: Streptococcus mutans, Streptococcus sobrinus, Streptococcus sanguinis, and Streptococcus gordoni. Researchers used four parafilm-stimulated saliva specimens – three from patients with dental caries and one without – to develop polymicrobial dental biofilms. L-arginine was found not to have a significant impact on the growth of the various strains of Streptococcus bacteria tested, however, L-arginine did inhibit the biofilm formation of S. mutans, which is considered one of the prime pathogens in dental caries. S. mutans biofilms grown with L-arginine also had lower exopolysaccharide/bacteria ratios when compared to samples that did not include L-arginine. These findings support L-arginine as a possible agent to help prevent dental carries.

Citation

New Gum Could Help Detect Peri-Implantitis

A team of researchers has begun formulating and testing a new chewing gum that would help to identify bacteria-causing inflammation, a leading cause of soft tissue and bone degeneration in peri-implant patients. The gum is engineered to react to specific salivary enzymes that are present when tissues become inflamed. In patients experiencing peri-implantitis, this reaction will lead to a breakdown in the gum, which will trigger a bitter taste in the patient’s mouth. Researchers compared their new gum to two existing tests that measure matrix metalloproteinases (MMPs), specifically MMPs -1, -8, and -9. The gum performed similarly or better than these existing tests and could eventually serve as an “anyone, anywhere, anytime” diagnostic test.

Citation

PPI use may Increase Risk for Osseointegrated Dental Implant Failure

A group of researchers from McGill University in Montreal, Quebec, Canada have recently published results of their study investigating the effect of proton pump inhibitors (PPIs) on osseointegrated dental implant failure. This retrospective cohort

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Experts Deem Biosimilars as Safe for Treating Rheumatic Disease

A multinational team of experts in rheumatology, dermatology, gastroenterology, pharmacology, regulation, and patients jointly evaluated the use of biosimilars in treating patients with rheumatic disease with the purpose of producing evidence-based statements on biosimilars. Of the 490 references identified, 29 papers were included in the review. This analysis resulted in five overarching principles and eight consensus recommendations related to biosimilars. These considerations span clinical trials, immunogenicity, indication extrapolation, switching between treatments, or interchangeability, and drug cost. Importantly, the group concluded that biosimilars are unlikely to have clinically meaningful differences when compared to the reference product.

Citation

Biologics-Induced Autoimmune Disorders on the Rise

The BIOGEAS Registry is an ongoing Spanish prospective cohort study, first started in 2002, investigating the long-term safety and efficacy of off-label use of biological agents in adult patients with severe autoimmune diseases. At the time of the study, the Registry contained 12,731 cases of biologic agent-induced autoimmune disease. In total, more than 50 different disorders have been reported, the most common of which are psoriasis (n=6,375), inflammatory bowel disease (n=845), and demyelinating CNS disease (n=803). The most common biologics involved in these cases were anti-TNF agents and immune check point inhibitors, which were identified in 9,133 and 913 cases, respectively. The authors believe that addressing unexpected immune disease, which affects 8 out of every 10,000 patients exposed to biologics, will become an increasingly difficult challenge to address in years to come as the use of biologics continues to rise.

Editor’s note: The Sjögren’s Syndrome Foundation Clinical Practice Guidelines for rheumatology and systemic disease, published in April 2017, covered the use of biologics in Sjögren’s. Anti-TNF agents were discouraged in Sjögren’s unless a patient’s Sjögren’s overlaps with rheumatoid arthritis or other conditions in which these therapies are indicated for inflammatory arthritis. Rituximab, however, was deemed to be of potential value for a number of systemic manifestations in Sjögren’s patients.

Citation

Study of Proton Pump Inhibitors and Osseointegrated Dental Implant Failure

Industry News

GSK-Insilico to Explore Artificial Intelligence as Part of Drug Discovery

GlaxoSmithKline (GSK) and Insilico Medicine have formed a new partnership to explore how Insilico’s artificial intelligence technology could help in the drug discovery process. Insilico, based at John’s Hopkins University’s Emerging Technology Centers, uses genomics, big data analysis and deep learning for drug discovery through computer modeling. This collaboration is one of several approaches by GSK to explore emerging technologies to help increase both efficiency and effectiveness when developing new medicines.

Shire Seeks Marketing Authorization for Lifitegrast in Europe

U.K.-based Shire Pharmaceuticals has applied for marketing authorization in Europe for lifitegrast, a treatment for dry eye disease (DED). Shire’s Xiidra®, a 5% lifitegrast ophthalmic solution, received FDA approval in July 2016 for the treatment of signs and symptoms of DED in U.S. adults. If approved, lifitegrast will be the first available LFA-1 antagonist to address symptoms of DED in European adults.

Nestlé and Enterome form Microbiome Diagnostic Partners

Nestlé Health Sciences has partnered with Enterome to create a new company – Microbiome Diagnostic Partners (MDP). This 50/50 joint venture will work to create innovative diagnostics across a broad range of health conditions related to the microbiome through a combination of the two company’s diagnostic development and commercialization programs. Greg Behar, CEO of Nestlé Health Science, said, “Microbiome Diagnostics Partners is equipped to lead diagnostic discovery in the microbiome field, opening the door to innovative therapeutic approaches combining diagnostics (Dx), nutritional therapies (Nx) and therapeutics (Rx).”

New Collaboration Focused on GPCR-Targeting Drugs

Heptares Therapeutics and PeptiDream have partnered to discover, develop, and commercialize therapeutics targeting an undisclosed G protein-coupled receptor (GPCR) suspected in inflammatory diseases. Heptares’ Stabilized Receptor (StaR®) technology will be used to generate 3D target structure information while PeptiDream will use its proprietary Peptide Discovery Platform System to identify and optimize peptides and small molecules for future development. The two companies will co-own any products that are developed through this partnership.

Johnson & Johnson Vision Acquires TearScience Inc.

Johnson & Johnson Vision has acquired TearScience Inc. as part of their strategy to further expand the company’s eye health portfolio. TearScience, a medical device manufacturer, focuses on evaluating and treating Meibomian gland health and dysfunction, a leading cause of dry eye disease. LipiFlow®, a product of TearScience, is the only FDA-approved medical device for Meibomian Gland Dysfunction that’s been shown to restore gland function. Financial terms for this acquisition have not been disclosed.

Shire Pharmaceuticals to Consolidate U.S. Offices

Shire Pharmaceuticals is consolidating their U.S. operations into two cities – Cambridge and Lexington, MA. The Cambridge site will be home to Shire’s rare disease research and U.S. commercial operations while biologic drug manufacturing and delivery system development and production will take place in Lexington. Shire’s global network includes nearly 14,000 employees across 17 sites in seven different countries. No significant reduction in the workforce is expected as a result of this move.
SSF Partner’s on new International Research Project – HarmonicSS

The SSF is proud to be a consortium partner on a new international research project – HarmonicSS. Officially titled HARMONIzation and Integrative Analysis of Regional, National and International Cohorts on Primary Sjögren’s Syndrome towards Improved Stratification, Treatment and Health Policy Making, the project launched in January 2017 with funding from European Union’s Horizon 2020 Research and Innovation program and the Swiss State Secretariat for Education, Research and Innovation. Through collaboration, participants envision an international network and alliance of partners and cohorts working to address the unmet need of primary Sjögren’s Syndrome while creating and maintaining a platform with open standards and tools, designed to enable secure storage, governance, analytics access control and controlled sharing of information at multiple levels along with methods to make results of analyses and outcomes comparable and sustainable across centers and associations.

SSF Participates in NHC Roundtable on Patient Representativeness

In May, SSF CEO Steven Taylor attended the National Health Council’s Roundtable on Defining Patient Representativeness. This meeting was convened to build a consensus around a common understanding of the term “representativeness” and how it can be applied to patient engagement activities as well as to develop a set of recommendations to address existing challenges to ensuring patient representativeness as a means to inform patient engagement strategies. When completed, the results of this meeting will be made available to the public and will include key points, conclusions, and next steps.

SSF Board Member Dr. Lawrence Ford Participates in AECR

This past June, Theresa Lawrence Ford, MD, FACR, and Chair of the SSF Clinical Trials Consortium, attended the Annual European Congress of Rheumatology, in Madrid Spain. Here Dr. Lawrence Ford presented her poster, titled “Exploration of Comorbidity Indices in Ethnic Minority Rheumatoid Arthritis Subsets.” The significance of this work is that the rheumatic disease comorbidity index and comorbidity count correlated well across ethnic groups, suggesting these comorbid indices may apply in relevant analyses of registry cohort data.

SSF Involvement at the 2017 Congress of Clinical Rheumatology

This past April, Frederick Vivino, MD, FACR, Chief, Rheumatology, Penn Presbyterian Medical Center; Director, Penn Sjögren’s Syndrome Center; and Professor of Clinical Medicine, Philadelphia, presented an “Update on Sjögren’s” at the 2017 Congress of Clinical Rheumatology in Destin, FL. Dr. Vivino, the former Chair of the SSF Medical and Scientific Advisory Board, discussed the challenges to diagnosing the disease and the burden of illness, how the classification criteria for Sjögren’s has evolved, and the role of Anti-SSB in diagnosing Sjögren’s. Dr. Vivino also discussed the SSF Clinical Practice Guidelines, covering the topics of fatigue, musculoskeletal pain, and the use of biologics to treat Sjögren’s.
Sjögren’s is an autoimmune inflammatory disease targeting exocrine glands, including the vestibular glands (vulva). Lymphocytic perivascular infiltration of predominately CD4+ T-helper cells can result in gland destruction and decrease in lubrication by glairy fluid. Vaginal dryness and itching, painful intercourse (dyspareunia) and frequent yeast infections contribute to decrease in QOL, including sexual dysfunction.

In addition to vaginal dryness (common), the following occur in Sjögren’s:

- Lichen planus and Lichen sclerosis
- Vaginal yeast infections
- Cervical dysplasia and cancer, especially in setting of HPV (human papilloma virus)
- Interstitial cystitis (~10%) | pelvic pain relieved by voiding; urgency, and frequency
- Endometriosis (4-fold increase) | pelvic pain around menses, excessive bleeding, back pain, painful urination
- Primary ovarian failure (20%) | premature menopause, infertility

Treatment Tips

- Topical estrogen products (vaginal cream, pill, ring) or systemic Hormone Replacement Therapy (HRT)
- Topical lubricants for dryness (see SSF Product Directory for a list of vaginal moisturizers)
- PAP or visual inspection (if prior hysterectomy) every 1-2 years; | PAP yearly and colposcopy for high risk patients
- Lichen planus or sclerosis may warrant topical steroids
- Antifungals (topical or oral) for frequent or severe vaginal yeast infections
- Refer to Urogynecologist for interstitial cystitis and pelvic pain symptoms
Submit an Abstract for the Next ISSS!

This symposium is designed to facilitate precision medicine practices in all aspects of clinical care, including patient diagnosis, prognosis, therapeutic responses, and prevention. Registration is now open for this 2.5 day conference, which will bring together representatives from science, technology, evidence-based medicine and leaders in the Sjögren’s/autoimmune research community to provide updates to an international audience, helping to narrow the gaps in knowledge.

Interested persons are encouraged to submit an abstract for the symposium by December 1, 2017. Eligible abstracts will describe original basic and clinical science related to the area of Sjögren’s or related diseases.

Dates & Location

Wednesday, April 18, 2018 4:00 PM – Saturday, April 21, 2018 12:00 PM
Capital Hilton Hotel, Washington, DC

Visit

http://tinyurl.com/ISSS2018

for the most up-to-date program and registration information.