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Sjögren's QUARTERLY

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The Professionals' Resource on Sjögren's

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Could Vagus Nerve Stimulation Improve Symptoms of Sjögren's?

Cranial nerve X, or the vagus nerve, is the major parasympathetic nerve of the autonomic nervous system. It comprises a bundle of ~80% afferent and ~20% efferent fibres necessary for the control of essential visceral functions such as gastrointestinal motility, secretions and heart rate.¹ Several homeostatic axes are innervated by the vagus nerve including the brain-gut axis, the hypothalamic-pituitary-adrenergic (HPA) axis and the cholinergic anti-inflammatory pathway (CAP).²⁻⁴ The vagus nerve is hypothesised to be a key modulator of each of these pathways and has been associated with immune regulation. Recent studies have provided evidence that stimulation of the vagus nerve (VNS) may provide therapeutic effects in immune-mediated inflammatory diseases (IMIDs). In Sjögren's, there is still an unmet need for pharmacological and non-pharmacological treatment

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Bio-therapeutics (or biologics), the fastest-growing sector in the pharmaceutical industry, are transforming medicine. These agents are instrumental in the management of autoimmune disorders and certain cancers, but also have multiple and increasing applications in eye care. Recently, the Anterior Segment Section of the American Academy of Optometry hosted a novel symposium highlighting biologic therapy, "Biologic Therapy: Applications in Anterior Segment Disease." The course provided an orientation to this class of medications, a discussion of the most commonly prescribed agents in medicine, and applications in ocular disease with an emphasis on disorders of the anterior segment. This event was moderated by Walt Whitley, OD, FAAO, chaired by Katherine M. Mastrota OD, FAAO, Diplomate, American Board of Optometry, and included panel speakers: Casey Hogan, OD, FAAO, FSLs, Diplomate, American Board of Optometry, Laura M Periman, MD, and David Scales, MD.

Biologic Therapy: Applications in Anterior Segment Disease

A Summary of An Anterior Segment Section Symposium Presented at the 97th Meeting of the AAO, 2018

The SSF thanks the participants of the symposium for authoring this article

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options.^{5,6}

The Cholinergic Anti-inflammatory Pathway

It has long been established that the vagus nerve provides a conduit between the central nervous system and peripheral immune system in a process known as the cholinergic anti-inflammatory pathway (CAP).⁷⁻⁹ Initially it was discovered that the vagus nerve senses peripheral inflammation and provides neural control of immune processes through the immune reflex.^{4,10,11} Later it was determined that acetylcholine (ACh) producing T cells are crucial for the anti-inflammatory effects of the vagus nerve signals of the CAP.¹²

The inflammatory reflex requires signals arising from both afferent and efferent arms of the vagus nerve. The afferent arm of the vagus nerve mediates communication between the immune system and the brain by sensing peripheral inflammatory mediators produced upon immune challenge, such as Interleukin (IL)-1 β and lipopolysaccharide (LPS). IL-1R and Toll-like receptor (TLR)⁴ on vagal afferents detect these inflammatory mediators and initiate afferent signalling.^{8,13} The afferent signals of the vagus nerve are relayed to the efferent arm of the vagus nerve via neuronal connections in the nucleus tractus solitarius (NTS) of the caudal medulla.¹⁴

The immunoregulatory activity of the vagus nerve is primarily mediated by the efferent arm. In the most widely accepted hypothesis of immunomodulatory vagus nerve signalling the efferent arm of the vagus nerve triggers catecholaminergic (noradrenergic) signalling from the splenic nerve via connections to the coeliac ganglion. Influence of the efferent arm of the vagus nerve on the spleen leads to release of ACh from splenic T cells with ACh-synthesising activity (choline-acetyl-transferase positive). ACh subsequently mediates

TNF α -suppressive effects upon macrophages via nicotinic ACh receptors (nAChR), specifically the α 7AChR9. Signals downstream from the α 7AChR result in inhibition of the nuclear translocation of NF κ B and reduced downstream pro-inflammatory cytokine production.¹⁵

The Hypothalamic-Pituitary-Adrenal Axis

In addition to the CAP, the vagus nerve is a key contributor to the neuro-immune axis, and is known to play a role in regulation of the HPA axis, which is integral to the control of metabolism, the immune regulation, sleep and, importantly, response to stress.² Dysregulation of the HPA axis is frequently associated with affective disorders which in turn are a common comorbidity of inflammatory disorders.¹⁶ It is now well-established that inflammatory cytokines, in particular IL-1 β , can activate the secretory activity of the HPA axis.¹⁷ There is evidence to suggest that vagus nerve stimulation may contribute to normalization of HPA axis function and amelioration of symptoms in chronic depression.^{18,19}

Vagus Nerve Stimulation

Vagus nerve stimulation was first used for treatment resistant epilepsy in 1988²⁰ and was FDA approved in 1997.²¹ Implanted vagus nerve stimulators are the most commonly used VNS devices. Electrodes surrounding the left cervical vagus nerve are controlled by a small prosthesis implanted in the upper chest.^{22,23} Vagus nerve stimulation increases activity in locus coeruleus and raphe nuclei, modulating norepinephrine and serotonin release, which amongst a diverse range of actions are known to mediate antiepileptic effects.²³

Whilst implanted VNS devices are well-tolerated and show promising results, the invasive procedure necessary to fit and service the device is not without risk.^{24,25} A non-invasive approach to VNS is therefore desirable and has led to the development of devices designed to stimulate the vagus nerve transcutaneously. Examples of non-invasive vagus nerve stimulators are the NEMOS and gammaCore devices. The gammaCore (nVNS) device comprises a hand held device which when placed at the site of the cervical vagus nerve has been used successfully to treat migraine and cluster headache.^{26,27} NEMOS (tvNS) is a device with an intra-auricular electrode, which stimulates the auricular branch of the vagus nerve and has been used successfully in cases of epilepsy.²⁸

Since their first use, implanted VNS devices have been trialled in several conditions including drug-resistant depression, anxiety and stroke. More recently however, both implanted and non-invasive VNS studies have covered a much more diverse range of diseases, ranging from traumatic brain injury, cardiovascular disease, diabetes and obesity.²²

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XiIDRA HAS BEEN STUDIED IN A LARGE DRY EYE DISEASE CLINICAL TRIAL PROGRAM

MORE THAN 2,500 PATIENTS ACROSS 5 CLINICAL TRIALS

STUDY 1

Studied 3 concentrations
(0.1%, 1.0%, 5.0%)

**230
PATIENTS**

**12
WEEKS**

STUDY 2

Phase 3

**588
PATIENTS**

**12
WEEKS**

STUDY 3

Phase 3

**718
PATIENTS**

**12
WEEKS**

STUDY 4

Phase 3

**711
PATIENTS**

**12
WEEKS**

SONATA

Phase 3

**331
PATIENTS**

**1
YEAR**

Xiidra is the first and only eye drop FDA-approved to treat both the signs and symptoms of Dry Eye Disease. It has been studied in more patients than any other pivotal clinical trial program for a prescription Dry Eye Disease treatment to date. Learn more about why you and your patients should give Xiidra a try.

Check out Xiidra-ECP.com

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.



BRIEF SUMMARY:

Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION

Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤ 3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose

tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data

Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg / day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.



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Multidisciplinary Teams for Clinical and Investigational Approaches to Sjögren's

An SSF-coordinated study group was recently held at the American College of Rheumatology's Annual Meeting in Chicago, IL, on Tuesday, October 23, 2019. Titled, "Multidisciplinary Teams for Clinical and Investigational Approaches to Sjögren's," this event was moderated by Nancy Carteron, MD, who was joined by Esen Akpek, MD, Frederick Vivino, MD, and Caroline Shiboski, DDS, MPH, PhD, who each provided perspectives from their given fields.

Dr. Vivino opened the session by discussing and highlighting the benefits of a multidisciplinary approach when developing Phase 1 of the Sjögren's Syndrome Foundation's Clinical Practice Guidelines in the U.S. These guidelines, which were created to improve the quality and consistency of care in the U.S., involved an arduous process that involved the consideration of clinical problems, surveys of patients and practitioners, the identification and prioritization of topics and the involvement of a variety of stakeholders, among other important steps. As a result of this effort, we now have a model for guidelines development, which is again being used for Phase 2 of this effort, and we have contributed to the increase in knowledge and awareness of Sjögren's among professionals and societies, expanded the network of Sjögren's providers in the U.S. and improved the quality and consistency of care in the U.S. for Sjögren's. Read more about Phase 2 of the SSF's Clinical Practice Guidelines in Volume 12, Issue 4 of *Sjögren's Quarterly*.

Next to speak was Dr. Akpek, who reviewed Sjögren's-related dry eye and extraglandular ocular manifestations of Sjögren's. Dr. Akpek noted that the repercussions from dry eye go beyond what many may think, and can include significant pain, limitations in performing daily activities, reduced vitality, poor general health and, oftentimes, depression. While reviewing dry eye and visual function it was recognized that dry eye slows down reading speed, which worsens with

prolonged reading – a factor that can have negative implications on a person's ability to work. Dr. Akpek also described studies which support that extraglandular ocular manifestations of Sjögren's may precede the diagnosis of Sjögren's, and encouraged that ophthalmologist consider assessing for Sjögren's in patients with clinically significant dry eye.

The final speaker of the day was Dr. Shiboski, who reviewed the oral complications of Sjögren's, the rheumatologist's role in helping to prevent these oral complications and an example of integrated care for Sjögren's patients. Complications discussed included dental caries, including the pathophysiology and preventive measures, severe salivary hypofunction, which is associated with dental caries and oral candidiasis and salivary gland enlargement. As this was a rheumatology meeting, Dr. Shiboski shared her thoughts on what can be done from a rheumatologist role to help prevent and address oral complications. It was suggested that Sjögren's patients, as well as rheumatoid arthritis, systemic lupus erythematosus and scleroderma patients, should be queried for having dry mouth. Any patient with dry mouth should be referred to a dentist for further evaluation and be prescribed a topical neutral sodium fluoride. Additionally, an oral soft tissue examination should be administered to rule out oral candidiasis and a five-minute whole saliva flow rate, both unstimulated and stimulated, could be useful in assessing the severity of the salivary hypofunction.

As an example of integrated care for Sjögren's patients, Dr. Shiboski spoke about her experience with The Sjögren's International Collaborative Clinical Alliance (SICCA), which was designed in part to create a data registry and biorepository for future studies. Involved patients were examined by a rheumatologist, ophthalmologist and oral medicine specialist during each

"VNS" Continued from page 1 ▼

There have now been several studies of vagus nerve stimulation in IMIDs other than Sjögren's, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and systemic lupus erythematosus (SLE). The results of these studies indicate VNS is well-tolerated and could be a novel, effective and safe non-pharmacological therapy for inflammatory diseases. VNS shows promise for the reduction of symptoms such as pain and fatigue where clinical improvement is consistent with a reduction in inflammatory markers. For a comprehensive review of the immune reflex and inflammatory diseases see the reference by Chavan et al, 2017.²⁹

VNS in Sjögren's

The cardinal symptoms of Sjögren's are salivary and lacrimal gland dryness and extraglandular symptoms such as pain and fatigue. In addition, anxiety and depression are highly prevalent. Although the etiology of Sjögren's is largely unknown, it is primarily attributed to chronic inflammation mediated by B cells and T cells. Inflammation is systemic, as demonstrated by raised levels of inflammatory cytokines in the peripheral blood.³⁰ There is growing evidence to suggest that inflammation is responsible for the extraglandular symptoms of Sjögren's³¹ alongside dysregulation of the HPA axis.³² We now know that the vagus nerve plays a role in the regulation of these processes, therefore harnessing the vagus nerve may be the key to improvement of extraglandular symptoms.

Recently, a study by our group sought to determine whether the use of non-invasive vagus nerve stimulation resulted in changes to peripheral inflammatory markers in fifteen participants with Sjögren's.³³ In our study, vagus nerve stimulation was delivered by the GammaCore (electroCore) device.

The participants had three visits over a 28-day study period. After an initial assessment, the subjects were trained to use the gammaCore device and continued to apply the nVNS dose twice daily for the study period. The electrodes of the device are placed on the skin with a small amount of conductive electrolyte gel at the expected position of the vagus nerve (over the carotid artery). The device delivers a 90 second dose of stimulation, which is applied consecutively to the right and left sides.

At visits one (Day 1) and three (Day 28) pre- and post- nVNS blood samples were drawn: before VNS and 90 minutes post- nVNS dose, respectively. At visit two (seven days after visit one), the subjects were asked to use the device 90 minutes prior to attending the unit when a post-nVNS sample was taken. Blood was drawn at each of these five time-points for assessment of inflammatory activity. In addition to blood draws, patient-reported outcome measures were recorded at each visit such that

differences in subjective symptom severity could also be assessed. Cytokine levels were assayed in the supernatants from whole blood stimulated with LPS and peripheral blood cell counts were assessed by flow cytometry.

Twelve out of 15 participants reported an improvement in their fatigue scores, with seven showing a $\geq 30\%$ reduction in fatigue within the 28 days. One participant did not report any improvement and two participants observed an initial improvement before returning to their baseline score at the final visit. None of the participants reported worsening of their symptoms and adverse events throughout the study were mild and transient.

We observed a significant reduction in physical fatigue, as measured using PRO-F 34, and daytime sleepiness³⁵ across three time-points ($p < 0.0003$ and 0.02 , respectively). Abnormal fatigue VAS, ESSPRI-Dryness and ESSPRI-Physical Fatigue subscales also showed trends of improvement.³⁶ There was very good concordance in the reported scores in three fatigue related questionnaires ($r = 0.82, 0.83, 0.72$, $p < 0.0001$).

The levels of MIP1 α , IL-1 β , TNF- α , IL-6 and IP-10 upon stimulation were significantly reduced across the five time-points. Additionally, TNF- α and IL-1 β levels were also significantly reduced after the first nVNS stimulation when compared to the baseline blood draw (time-points one and two). However, this was not replicated in the pre- and post-VNS blood draws after 28 days of device use (time-points four and five).

The numbers of T cells, NK-cells and NKT-cells increased after the first application of nVNS at visit one. Linear regression of the change in PRO-F score versus baseline cell subset numbers showed a positive relationship between the total improvement in fatigue score and NK-cell and T cell counts at baseline.

Discussion

Over the last two decades, several prominent groups have been working towards a better understanding of neuro-immune communication, however, only recently has vagus nerve stimulation been considered as a therapeutic opportunity in immune mediated diseases.

To our knowledge our study was the first attempt to detect biological effects of nVNS in Sjögren's. Our observations indicated that nVNS might reduce subjective symptoms of physical fatigue and sleepiness in a short time frame. Consistent with these improvements in fatigue was a decrease in LPS induced pro-inflammatory cytokine production by peripheral immune cells.

Baseline T cell and NKT-cell numbers positively correlated with improvement in fatigue scores. This may be of significance since it is known that acetylcholine-producing T cells are an essential component of the CAP.



Clinical News: Rheumatology

Severe Systemic Disease May be Predicted by Disease Onset

Early-onset Sjögren's has been found to be associated with features that are predictive of severe systemic disease. Specifically, patients diagnosed during early onset ($n=55$), defined as a diagnosis at or prior to 35 years, presented with a significantly higher frequency of salivary gland enlargement (47.2% vs 33.3%, $P=0.045$), adenopathy (25.5% vs 11.8%, $P=0.006$), purpura (23.6% vs 9.2%, $P=0.002$) and renal involvement (16.4% vs 4.4%, $P=0.003$) compared to patients diagnosed at later terms. Additionally, the early-onset patients had a higher frequency of hypergammaglobulinaemia (60.8% vs 26.6%, $P<0.001$), RF positivity (41.5% vs 20.2%, $P<0.001$), low C3 level (18.9% vs 9.1%, $P=0.032$), low C4 level (54.7% vs 40.2%, $P=0.048$) and autoantibodies [84.6% with anti-SSA vs 54.4% ($P<0.001$) and 57.7% with anti-SSB vs 29.7% ($P<0.001$)]. Significant differences were seen in changes in ESSDAI scores at baseline and 5-years, with early-onset patients fairing worse (0.72, $P=0.27$) and later-onset patients showing improvements (-1.27, $P<0.0001$) during this time frame ($P=0.005$).

Citation

Angquetil C et al. Is early-onset primary Sjögren's syndrome a worse prognosis form of the disease? *Rheumatology (Oxford)*. 2018 Dec 17. doi: 10.1093/rheumatology/key392. [Epub ahead of print].

Fatigue and More Improved in Sjögren's Through Supervised Walking Program

A supervised walking program was found to be safe and feasible and showed improvements in cardiorespiratory

fitness, exercise tolerance, fatigue and patient perception of improvement in Sjögren's patients. Forty-five sedentary Sjögren's patients were divided into two groups, the treatment group ($n=23$), which participated in supervised walking three times per week for 16 weeks, and a control group ($n=22$), which did not perform any type of regular physical exercise. Investigators assessed VO2max, ESSDAI, hematological tests and the SF-36 at baseline and week 16 of the study. Additionally, ESSPRI, Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-Fatigue), and Beck Depression Inventory (BDI) were measured prior to the intervention and again at 8 and 16 weeks. After 16 weeks, the mean change of VO2max (ml/kg/min), distance, and FACIT-Fatigue were higher in the treatment group than in the control ($p=0.016$, $p=0.043$ and $p=0.030$, respectively). Improved cardiorespiratory fitness was associated with improvements in fatigue scores and physical components of quality of life (SF-36). Furthermore, improved fatigue scores were associated with reduced depression and improvements in the physical and mental components of SF-36. Overall, 95.4% of patients in the treatment group rated themselves as clinically improved versus 62% of the patients in the control group ($p=0.049$). Importantly, there was no flare in disease activity and no serious adverse events with exercise.

Citation

Miyamoto ST et al. Supervised walking improves cardiorespiratory fitness, exercise tolerance, and fatigue in women with primary Sjögren's syndrome: a randomized-controlled trial. *Rheumatol Int*. 2019 Jan 2. doi: 10.1007/s00296-018-4213-z. [Epub ahead of print].

Decreased Levels of IL-35 Seen in Sjögren's Patients

Based on results from a recent study, investigators have concluded that a decrease in IL-35 levels may play an important role in the pathogenesis of Sjögren's and that IL-35 may act as a potential therapeutic agent

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Therefore, evaluation of the relationship between the number of baseline acetylcholine-producing T cells and improvement in fatigue scores in response to nVNS is essential for our understanding of the response to VNS in Sjögren's.

Our initial study in Sjögren's is limited by the lack of a sham-device control group as improvements in subjective fatigue levels could be attributed to placebo effect. However, objective biological changes in cytokine production and cell numbers were also observed during the study period, which are less likely to be caused by a placebo effect. A follow up study with a sham-device control group is ongoing to provide validation of these preliminary findings.

Whilst the results of VNS in multiple IMIDs are promising, the neuro-immune communication thought to be involved has not been fully characterized. It is unclear whether improvements in symptoms such as fatigue, anxiety and depression are due to reduced inflammation, regulation of the HPA axis or a complex interplay of both.

Studies of VNS in immune-mediated diseases have revealed many exciting avenues for future research. The role of the immune microenvironment at sites of vagus nerve innervation, the effects of VNS on the HPA axis in the context of chronic inflammation and neural-immune adaptations to long-term VNS are sources for further investigation. ■

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"Clinical News" Continued from page 7 ▼

against inflammation in Sjögren's patients. Compared to healthy controls (n=34), Sjögren's patients (n=34) had significantly lower plasma IL-35 levels, P35 and EBI3 mRNA levels and percentages of CD4+ EBI3 + T cells. Conversely, Sjögren's patients had increased percentages of CD19 + EBI3 + B cells when compared to healthy controls. Investigators observed negative correlations between ESSDAI scores and IL-35 levels, EBI3 mRNA expression and the percentage of CD4+ EBI3 + T cells, while IL-35 and EBI3 mRNA were negatively correlated with the erythrocyte sedimentation rate. Notably, Sjögren's patients who were positive for anti-SSB antibodies presented with lower IL-35 levels and percentages of CD4+ EBI3 + T cells.

Citation

Guo J, Gu M, Zhang W, Liu Y, Qian C & Deng A. Aberrant IL-35 levels in patients with primary Sjögren's syndrome. *Scand J Immunol*. 2018 Nov;88(5):e12718. doi: 10.1111/sji.12718.

Usefulness of ¹⁸F-FDG PET for Diagnosing Lymphoma in Sjögren's

Using ¹⁸F-FDG positron emission tomography with computed tomography (PET-CT), investigators found that lymph node and parotid gland involvement are commonly observed at similar frequencies in Sjögren's patients with and without lymphoma. PET-CT scans were compared for Sjögren's patients with (n=15) and without lymphoma (n=30) and found that those with lymphoma had larger parotid glands, on average (p=0.048), as well as higher maximum standard uptake values (SUVmax) in the parotid glands when compared to those without lymphoma. Lymph node FDG uptake was observed in a greater proportion of patients with lymphoma (53.3%) compared to patients without lymphoma (43.3%), as was focal pulmonary uptake (nodules or condensations), which was observed in five patients with lymphoma and only one without. Notably, an SUVmax of the parotid gland ≥ 4.7 and/or the presence of focal pulmonary lesions was highly suggestive of lymphoma (sensitivity = 80%, specificity = 83.3%). This retrospective study involved two centers and included Sjögren's patients who had undergone PET-CT.

Citation

Keraen J et al. Usefulness of 18 F-FDG Positron Emission Tomography (PET) for the diagnosis of lymphoma in primary Sjögren's syndrome. *Arthritis Rheumatol*. 2019 Jan 7. doi: 10.1002/art.40829. [Epub ahead of print]

Combination Therapy of LEF/HCL Shown to be Effective Against Sjögren's

Outcomes supporting the clinical efficacy of leflunomide (LEF) and hydroxychloroquine (HCL) combination therapy for treating Sjögren's were recently presented at the 2018 Annual Meeting of the American College of

Rheumatology. Investigators found that over a 24-week period, Sjögren's patients receiving 20mg of leflunomide (LEF) daily and 400mg of hydroxychloroquine (HCL) twice daily (n=21) showed significant improvements in both primary and secondary outcomes when compared to Sjögren's patients receiving a double placebo (n=8). Specifically, ESSDAI scores at 24 weeks compared to baseline revealed significant improvements in the treatment group (baseline: 11.8; p=0.044, n=9 responders with ESSDAI decrease ≥ 3) compared to the placebo group (baseline: 11.5; p=0.818, 1 responder). The treatment group also showed significant improvements in oral dryness (SWS from 823 to 1366 μ l/5 minutes, p=0.04) while the placebo group showed a decline (SWS from 1125 to 815 μ l/5min, p=0.169). Additionally, significant improvements were seen in ESSPRI, ESSPRI Pain, ESSPRI Fatigue, Physician's Global Assessment and Patient's Global Assessment in the treatment group (all at least p<0.05) but not in the placebo group. The authors note that larger randomized controlled trials are needed to confirm these findings and identify potential biomarkers.

Citation

Radstake TRDJ et al. Clinical efficacy of leflunomide/hydroxychloroquine combination therapy in patients with primary Sjögren's syndrome: results of a placebo-controlled double-blind randomized clinical trial. 2018 American College of Rheumatology Annual Meeting, Oct. 2018.

High Percentage of Fibromyalgia Patients Test Positive for Sjögren's Autoantibodies

A recent analysis found that nearly one-third of fibromyalgia patients tested positive for a Sjögren's biomarker, and of that group, the majority tested positive for at least one tissue specific autoantibody. Fibromyalgia patients (n=185) were tested for either the classic autoantibodies (SS-A/Ro, SS-B/La, ANA and RF) and early tissue specific autoantibodies (SP-1, CA6, PSP) (n=151) or just the early tissue specific autoantibodies (n=34). In the group of 151 patients, 49 tested positive for Sjögren's autoantibodies, with four testing positive for the classic Sjögren's markers, 40 testing positive for early Sjögren's markers and five testing positive for both the early and classic markers. In the group of 34, 10 patients tested positive for early Sjögren's markers. Across both groups, 55 patients were positive for the early markers (SP-1, CA6, PSP). Specifically, 83.6% were positive for SP-1, 12.7% were positive for CA6 and 20% were positive for PSP. Notably, 14.5% of these patients were positive for more than one early marker.

Citation

Applbaum E & Lichtbroun A. Novel Sjögren's autoantibodies found in fibromyalgia patients with sicca and/or xerostomia. *Autoimmun Rev*. 2018 Dec 17. pii: S1568-9972(18)30293-3. doi: 10.1016/j.autrev.2018.09.004. [Epub ahead of print].

"Biologic Therapy" Continued from page 1 ▼

Background on Biologics and Biosimilars

Dr. Hogan set the stage by reviewing the basics and background of biologic medicines. The U.S. Food and Drug Administration (FDA) defines a biologic as a product that can be a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings." The FDA definition of biosimilars was also discussed, noting that they are defined by the FDA as biologic products that are "highly similar to an FDA-approved biologic product, known as a reference product, notwithstanding minor differences in clinically inactive components, and that there can be no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency." Biologics are macromolecules that are more complex in structure, identical copies are not reproducible, and they are highly sensitive to external conditions and environmental changes. Biologics have a higher immunogenic potential, and this is critical for clinicians to consider when prescribing bio-therapeutics for their patients.

The Role of Biologic Therapy in the Management of Sjögren's

Eye care providers are often the first-line providers that undiagnosed Sjögren's patients seek for care. Ocular manifestations of Sjögren's are well-established and clinical practice guidelines, developed by the Sjögren's Syndrome Foundation (SSF) to aid clinicians in the consistency of care for their patients, provide guidance for ocular management as well as systemic disease.

Biologic therapies, such as rituximab (RTX), may continue to play a vital role in the management of Sjögren's as more research continues. At the present time, biologic therapies such as RTX should only be considered in patients with serious organ manifestations who fail other conservative treatments. According to SSF clinical practice guidelines for rheumatology, RTX may be considered as a therapeutic option in adults with Sjögren's with any or all of the associated systemic manifestations, including pulmonary disease, inflammatory arthritis, cryoglobulinemia associated with vasculitis, peripheral neuropathy, and severe parotid swelling. RTX may be considered as a therapeutic option for keratoconjunctivitis sicca in patients with Sjögren's when all other conservative treatments have failed, however, this is considered a weak recommendation (based on less than or equal to six months of Schirmer's outcomes).

The presenters called for expanded ocular surface testing and evaluation metrics in order to improve evaluating the efficacy of biologics in the management

of Sjögren's-associated ocular surface disease. The value of RTX treatment in Sjögren's is predicated on the well-established role of B cell hyperactivity in the immunopathogenesis of the disease. Inconsistency has been shown between studies in the clinical outcomes of RTX use, with some studies not meeting primary endpoints and others showing beneficial effects. The positive effects seen, no doubt, will lead to better study designs, response predictors, improved outcome metrics and continued emphasis on understanding the role biologics and concomitant T cell modulatory therapies play in reducing the morbidity of ocular surface disease.

Immunopathophysiology and Biologic Therapy: Applications in Anterior Segment Disease

Dr. Laura Periman, globally recognized as an expert in immunology and ocular surface disease, reviewed the immunopathology behind anterior segment disease. She described the immune system as an exquisitely complex, dynamic and fine-tuned system of checks and balances, detailing the important role of innate and adaptive immunity in ocular surface disease. Normal and healthy processes include: 1) initiation with pro-inflammatory cytokine release; 2) amplification and signaling to the local-regional lymph node; 3) T cell differentiation and proliferation; 4) migration, activation and recruitment of T cells; and 5) resolution, immunoregulation and return to homeostasis. Loss of homeostatic and immunoregulatory control ultimately leads to ocular tissue destruction and damage to the lacrimal functional unit (LFU) in the patient suffering from Sjögren's and DED.

Specific Therapeutic Strategies: How Biologics Work

In general terms, Dr. Periman reviewed therapeutics in four major categories: immuno-antagonist (e.g. Rituxan, etanercept and lifitegrast), immunosuppressants (e.g. steroids and Methotrexate), immuno-modulators (e.g. cyclosporine A and corticotropins); as well as new classes (e.g. gene therapy and co-stimulatory signal blockers like lifitegrast and abatacept). She then focused on how biologic therapies work by addressing dysfunctional and dysregulated immunologic processes including: cytokine function, production, and signal transduction; suppression of feedback loops; limiting T cell proliferation and T cell activation; as well as the therapeutic importance of B cell depletion for Sjögren's patients. Specific therapeutic strategies reviewed were interference with cytokines via TNF (tumor necrosis factor) inhibitors like etanercept or infliximab, limiting T cell activation with biologic agents including abatacept, or B cell depletion by biologic agents such as RTX or belimumab. Even after effective B cell depletion therapy,

an active T cell management strategy with topical medications (e.g. tacrolimus, cyclosporine A and lifitegrast is likely necessary for ocular symptoms in Sjögren's.

The Role of the Immune System and Dry Eye Disease in Sjögren's

Loss of homeostasis and regulatory control of the immune system is the key driver behind DED in the Sjögren's patient. CD4+ Th1 and Th17 cells are the primary T cells implicated in both DED and Sjögren's. CD8+ cells suppress the Th17 response and suppress Th17-induced barrier disruption. CD8+ are decreased in DED. T-regulatory cells may be defective in function or be of insufficient quantity in patients with DED and Sjögren's.

The immune response involves a complex interaction between innate and adaptive immunity and the cells unique to each. Lymphocytes (T cells and B cells) play critical roles in shaping immune responses in both healthy individuals, healthy response to injury and people with Sjögren's. Advancements in the fields of DED and Sjögren's have expanded the immunotherapeutic options for patients with DED and Sjögren's. Eye care will see more impacts from commonly prescribed immunobiological therapies. Dr. Periman looks forward to the development and clinical point-of-care availability of advanced tear diagnostics to help accurately discern the particular complex of T cell and B cell dysregulation for Sjögren's patients. This, in turn, may help in tailoring therapies to individual patients.

Biologics in the Treatment of Non-Infectious Uveitis (NIU)

Dr. David Scales, a specialist in the management of recalcitrant non-infectious uveitis (NIU) cases often seen associated with inflammatory or autoimmune diseases, presented on the use of biologics in the treatment of NIU. Biologics were originally considered second or third-line treatment options, but for Dr. Scales and others, they are a first-line choice for immunomodulatory treatment or IMT (following steroid pulse to control active inflammation). There is a need for immune modulating agents in the management of NIU. NIU is a group of ocular inflammatory end-organ diseases resulting from immune-mediated processes and cytokine-mediated disease modulated by the CD20 molecule, IL-17, IL-23, and TNF- α . The immunomodulating biologic drugs considered in the treatment of NIU would include TFN- α inhibitors such as adalimumab, infliximab, or abatacept. Anti-CD20 monoclonal antibodies such as RTX are also employed. Traditionally, corticosteroids have been standard therapy for NIU due to their efficacy, rapid onset of action, and they are titratable. However, Dr. Scales emphasized that all clinicians are

familiar with the high incidence of local ocular side effects and systemic complications from chronic steroid therapy, which pushes biologic therapies to the first-line steroid sparing or IMT option.

A typical course of action utilizing biologic agents in the treatment of NIU would include suppression of inflammation with oral steroids while starting the biologic agent. Most cases would include the initiation of 1 mg/kg initial dose, followed by a 4-6-week taper after the NIU is controlled. Most immunomodulating agents, including biologic therapy, need 4-6 weeks for onset of action.

Management Considerations in Biologics and NIU

Management considerations in biologics and NIU would include testing for TB and hepatitis (exclude), rule out multiple sclerosis and history of optic neuritis, and, if in doubt, obtain an MRI of a brain/neurology consult. It is important for clinicians to understand the risk of heart failure development or worsening, and always coordinate care with internal medicine, rheumatology, hematology, and others. Table 1 reviews potential complications of biologics used in NIU.

Table 1: Potential complications of biologics used in NIU

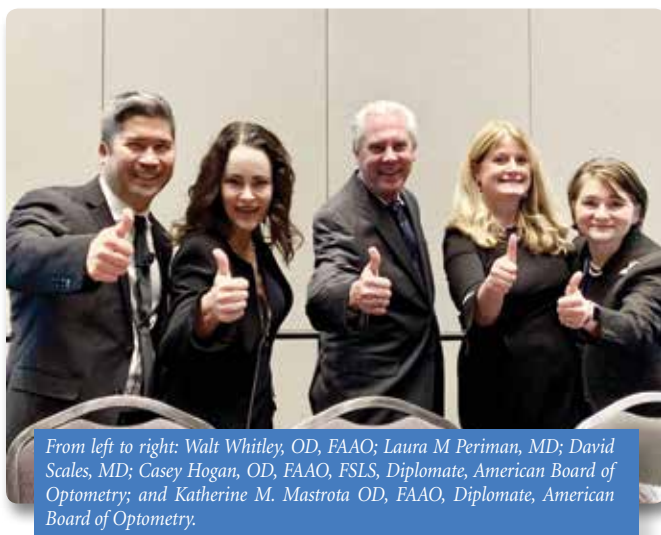
- Rash/allergic reaction
- Immune reactions (lupus like)
- Development of severe infections
- Liver dysfunction
- Blood dyscrasias
- Heart failure development or worsening
- Activation/reactivation of TB
- Multiple sclerosis activation/reactivation
- Immunosuppression and increased risk of infection
- Risk of developing malignancy

Summary

In conclusion, biologics are an important class of medications to treat Sjögren's and DED, NIU, and other anterior segment diseases. Adalimumab is now FDA approved for the treatment of NIU. Look for new studies to expand treatment modalities, including novel B cell depletion therapies. Active research is ongoing to evaluate new alternative treatments and to improve study designs with the end goal to improve the quality of life of patients who suffer from these often challenging-to-treat and recalcitrant diseases.

"Biologic Therapy" Continued from page 11 ▼

The esteemed American Academy of Optometry held their 97th annual meeting, Academy 2018 San Antonio, during the month of November at the Henry B. Gonzalez Convention Center in San Antonio, Texas. The goal of the annual meeting that attracts eye care providers from around the globe is to maintain and enhance excellence in optometric practice, by both promoting research and the dissemination of knowledge. Learn more about the AAO and their upcoming meetings by visiting <https://www.aaopt.org/>. ■



From left to right: Walt Whitley, OD, FAAO; Laura M Periman, MD; David Scales, MD; Casey Hogan, OD, FAAO, FSLs, Diplomate, American Board of Optometry; and Katherine M. Mastrota OD, FAAO, Diplomate, American Board of Optometry.

Impact of Smoking and Obesity on Risk for Sjögren's

A new case-control study has found that current smokers were less likely to have Sjögren's (OR 0.34, 95% CI 0.14-0.85), while no association between former smoking activity and Sjögren's was seen when compared to those who had never smoked (OR 1.27, 95% CI 0.80-2.03). Smoking status had no association with antinuclear antibody, anti-SSA, anti-SSB, or rheumatoid factor positivity ($p > 0.05$). Additionally, no associations were seen between body mass index and Sjögren's (OR 0.79; 95% CI 0.48-1.30).

Editor's Note: The negative association between current smoking and Sjögren's is in line with the findings from the study summary, "Impact of Smoking and SES on Risk for Sjögren's Diagnosis"; found in Vol. 13, Issue 4 of Sjögren's Quarterly. However, the previously published study had noted an increased risk for Sjögren's with former smoking activity, while the summary above notes that no associations were found.

Citation

Servioli L et al. Association of smoking and obesity on the risk of developing primary Sjögren syndrome: a population-based cohort study. *J Rheumatol*. 2019 Jan 15. pii: jrheum.180481. doi: 10.3899/jrheum.180481. [Epub ahead of print].

"Multidisciplinary Teams" Continued from page 5 ▼

visit. This model of integrated care proved effective for performing the multidisciplinary work-up required for establishing a reliable Sjögren's diagnosis. However, Dr. Shiboski acknowledged that this type of set-up may be difficult to replicated due to the complexities that exist related to health insurance coverage in the U.S.

As in previous years, the SSF is grateful to the American College of Rheumatology for approving this important study group, and, of course, to the speakers who took the time to participate and share their perspectives and expertise. ■



From left to right: Nancy Carteron, MD; Frederick Vivino, MD; Esen Akpek, MD; and Caroline Shiboski, DDS, MPH, PhD, at ACR's 2018 Annual Meeting, Chicago, IL.

Mesenchymal Stem Cell Use Found Safe in Autoimmune Patients

Data from a retrospective study on mesenchymal stem cell infusion shows support for its use as a safe therapy in patients with autoimmune diseases. Survival rates at 5- and 8-years were 90.4% and 88.9%, respectively, with deaths occurring in 45 patients, the most common cause of which was disease relapse and complications associated with the underlying disease. Importantly, the incidence rate of infections was 29.5%, with serious infections being noted at 12.9%. Additionally, five patients experienced malignancies. A total of 404 autoimmune disease patients who had received mesenchymal stem cell infusions between 2007 and 2016 were included in this study. The most common indications for infusion were Sjögren's, systemic lupus erythematosus and systemic sclerosis with the majority of stem cells used coming from the umbilical cord.

Editor's Note: Mesenchymal stem cells are multipotent stem cells, found in bone marrow, that play an important role in producing and repairing skeletal tissues, including cartilage, bone and lipids found in bone marrow. Research is ongoing in the evaluation of these cells' ability to reduce

inflammation, slow autoimmune disease progression and more.

Citation

Liang J et al. Safety analysis in patients with autoimmune disease receiving allogeneic mesenchymal stem cells infusion: a long-term retrospective study. *Stem Cell Res Ther.* 2018 Nov 14;9(1):312. doi: 10.1186/s13287-018-1053-4.

Breast Implants Associated with Higher Rates of Sjögren's, Other Autoimmune Diseases

A large U.S. Food and Drug Administration post-approval study has found that silicone breast implants are associated with higher rates of Sjögren's (standardized incidence ratio [SIR] 8.14), scleroderma (SIR 7.00), rheumatoid arthritis (SIR 5.96), stillbirth (SIR 4.50), and melanoma (SIR 3.71) when compared to normative data. This study used prospective monitoring of long-term implant-related outcomes and systemic harms for silicone or saline implants from Allergan and Mentor, placed for primary/revision augmentation or reconstruction. A total of 99,993 patients were included in this study.

Citation

Coroneos CJ, Selber JC, Offodile AC 2nd, Butler CE, Clemens MW. US FDA breast implant postapproval studies: long-term outcomes in 99,993 patients. *Ann Surg.* 2018 Sep 14. doi: 10.1097/SLA.0000000000002990. [Epub ahead of print]

H. Pylori More Prevalent in Sjögren's Compared to Controls

A comparison of Sjögren's patients (n=43) and healthy controls (n=95) revealed that those with Sjögren's had a higher prevalence of *H. pylori* infection compared to the general population. Serum levels of IgM (34.9% vs 10.5%, $p=0.001$) and IgA (67.4% vs 46.3% $p=0.021$) anti *H. pylori* antibody were significantly higher in Sjögren's patients compared to the control group and there was a positive correlation between age and *H. pylori* infection ($r=0.2$, $p=0.05$). Investigators used ELISA to determine serum levels of IgA and IgM anti *H. pylori* antibody.

Citation

Saghafi M, Abdolahi N, Orang R, Hatef MR & Molseghi MH. Helicobacter pylori infection in Sjögren's syndrome: Co-incidence or causality? *Curr Rheumatol Rev.* 2018 Nov 12. doi: 10.2174/1573397114666181113102427. [Epub ahead of print].

Increased Rates of H. Pylori Infection Seen in Sjögren's

A meta-analysis evaluating the association between *H. pylori* and Sjögren's found that Sjögren's patients (n=619) had a significantly higher rate of infection compared to the control group (n=1,339) (OR=1.19, 95% CI: 1.01-1.41, $P=.033$). Combined, the total prevalence of *H. pylori* infection was 53.83% (1054/1958), with group prevalence rates of 63.65% (394/614) for Sjögren's patients and 42.29% (660/1339) for controls. In all, nine studies accounting for 1,958 individuals with data on *H. pylori* infection were included.

Citation

Chen Q, Zhou Z, Tan W & Zhang M. Association between Helicobacter pylori infection and Sjögren syndrome: A meta-analysis. *Medicine* (Baltimore). 2018 Dec;97(49):e13528. doi: 10.1097/MD.00000000000013528.



Clinical News: Cardiovascular

Risk for Venous Thrombosis Identified in Sjögren's

Investigators have concluded that Sjögren's patients are potentially at higher risk for venous thrombosis, with interstitial lung disease and anti-SSA positivity increasing that risk. A total of 16 Sjögren's patients were included in this retroactive study, 14 of which had lower extremity venous thrombosis while the remaining two had jugular vein thrombosis. At admittance, 12 patients had symptoms of dryness and four had pulmonary symptoms. All cases in this study were found to have interstitial lung disease and 12 of the 16 cases were anti-SSA positive. Notably, the authors found that patients were negative for antiphospholipid antibodies, which are normally associated with blood clotting in autoimmune populations.

Citation

Zhang YF & Lu YW. Clinical features of patients with primary Sjögren's syndrome complicated with venous thrombosis. *Zhonghua Yi Xue Za Zhi.* 2018 Oct 23;98(39):3197-3199. doi: 10.3760/cma.j.issn.0376-2491.2018.39.014.

Sjögren's Associated with Increased Cardiovascular Morbidity

Investigators have concluded that Sjögren's is associated with an increase in cardiovascular morbidity and suggest Sjögren's patients be screened by a cardiologist for cardiovascular comorbidities for preventive interventions as part of a multidisciplinary approach. In a meta-analysis, it was found that Sjögren's patients, when compared to controls, were at a significantly increased risk for coronary morbidity (RR=1.34, 95%CI: 1.06-1.38; $p=0.01$), cerebrovascular morbidity (RR=1.46, 95%CI: 1.43-1.49, $p<0.00001$), heart failure rate (odds ratio=2.54, 95%CI: 1.30-4.97, $p<0.007$), and thromboembolic morbidity (RR=1.78, 95%CI: 1.41-2.25, $p<0.00001$). However, there was no statistically significant increased risk of cardiovascular mortality (RR=1.48, 95%CI: 0.77-2.85, $p=0.24$). A total of 484 articles were identified from the MEDLINE and COCHRANE databases in addition to abstracts from recent meetings held in the U.S. and Europe. Fourteen of these articles, involving 67,124 Sjögren's patients, were included in the study.

"Clinical News: Cardiovascular" Continued from page 13 ▼

Citation

Beltai A et al. Cardiovascular morbidity and mortality in primary Sjögren syndrome: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2018 Dec 20. doi: 10.1002/acr.23821. [Epub ahead of print]



Clinical News: Oncology

Lymphoma Diagnosis Precedes Sjögren's Diagnosis in Large Percentage of Patients

Investigators found that Sjögren's remains undiagnosed until after lymphoma diagnosis in a substantial number of patients, particularly men. Being male (39% vs 10%, $p=0.006$), enlarged lymph nodes during the disease (61% vs 27%, $p=0.01$), mucosa-associated lymphoid tissue (MALT) lymphoma (50% vs 22%, $p=0.02$), and salivary gland lymphoma (61% vs 26%, $p=0.006$) were more common in patients with a pre-existing lymphoma at Sjögren's diagnosis compared to those without. Sjögren's patients with a diagnosis of malignant lymphoma ($n=224$) before or after their Sjögren's diagnosis were identified by linking the Swedish Patient Register (1964-2007) with the Cancer Register (1990-2007).

Citation

Vasaitis L. Comparison of patients with and without pre-existing lymphoma at diagnosis of primary Sjögren's syndrome. *Scand J Rheumatol*. 2018 Nov 13:1-6. doi: 10.1080/03009742.2018.1523456. [Epub ahead of print]



Clinical News: Ocular

Clinical Severity of DE and Salivary Gland Dysfunction Predicted by Phenotypic Features

Recent findings support that Sjögren's patients with positive rheumatoid factor (RF) or an ANA $\geq 1:320$ at baseline could benefit from regular ophthalmology examinations, even if they did not originally show symptoms of dry eye. Investigators categorized Sjögren's patients ($n=134$) into four groups based on their Schirmer test value (STV) and severity of salivary gland dysfunction, which was based on unstimulated whole salivary flow rate. The three groups included those with an abnormal STV and moderate-to-severe salivary gland dysfunction (AB-STV/MS-SGD; $n=105$), abnormal STV and minor salivary gland dysfunction (AB-STV/Mi-SGD; $n=16$) and normal STV and moderate-to-severe salivary gland dysfunction (N-STV/MS-SGD; $n=13$). Notably, those

in the AB-STV/Mi-SGD group were younger and had lower Xerostomia Inventory Scores and lower levels of $\beta 2$ -microglobulin. The N-STV/MS-SGD group had less hyperimmunoglobulinemia, RF and ANA. At two-year follow-up, positive RF or an ANA $\geq 1:320$ at baseline were more likely to have abnormal STV. This study included 134 patients from the KISS cohort.

Citation

Koh JH, Lee J, Chung SH, Kwok SK & Park SH. Phenotypic features and predictors of the clinical severity of keratoconjunctivitis sicca and salivary gland dysfunction in patients with Sjögren's syndrome: a longitudinal analysis of the Korean Initiative of primary Sjögren's Syndrome (KISS) cohort. *Scand J Rheumatol*. 2018 Nov 26:1-9. doi: 10.1080/03009742.2018.1504982. [Epub ahead of print]

Individual DE Tests Unable to Detect Differences Between Diseases

Despite being distinguishable conditions, investigators found that a single ocular tool was unable to detect differences in the signs and symptoms of dry eye disease between patients with Sjögren's ($n=98$), graft-versus-host disease ($n=28$), Graves orbitopathy ($n=28$), diabetes mellitus ($n=11$), glaucoma under treatment with benzalkonium chloride medications ($n=17$) and healthy controls ($n=24$). Upon analysis, the most important variable for classification was the Ocular Surface Disease Index followed by tear film break-up time and corneal fluorescein staining. Additionally, investigators examined differences between primary ($n=57$), secondary ($n=41$) and non-Sjögren's ($n=32$). Here, only 54.6% of the patients were identified correctly using the combined accuracy of the tests.

Citation

Garcia DM et al. Is Sjögren's syndrome dry eye similar to dry eye caused by other etiologies? Discriminating different diseases by dry eye tests. *PLoS One*. 2018 Dec 3;13(12):e0208420. doi: 10.1371/journal.pone.0208420. eCollection 2018.

In Vivo Confocal Microscopy Found Reliable in Corneal Epithelium Evaluation

In vivo confocal microscopy (IVCM) was found to be a reliable technique for examining the corneal epithelial microstructural changes associated with dry eyes as well as objectively and reproducibly quantifying cell densities within all corneal epithelial layers. Patients with clinically diagnosed aqueous tear-deficient dry eyes were studied, including those with non-Sjögren's dry eye ($n=12$; 22 eyes), Sjögren's dry eye ($n=22$; 44 eyes) and healthy controls ($n=10$; 7 eyes). When compared to controls, both the non-Sjögren's dry eye ($p<0.05$) and Sjögren's dry eye ($p<0.01$) groups showed a decrease in the density of superficial epithelial cells. The density of the outer layer of wing cells was lowest in the Sjögren's dry eye group ($p<0.01$), however, the density of basal epithelial cells was lower in both the non-Sjögren's dry eye and Sjögren's dry eye groups when compared

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Industry News

Aurinia's VOS Shows Superior Effectiveness Against Competitor in Phase II Trial for DES Treatment

Aurinia Pharmaceuticals Inc., a clinical stage biopharmaceutical company, has announced positive results for a Phase II head-to-head study evaluating the efficacy, safety and tolerability of their product, voclosporin ophthalmic solution (VOS) 0.2% compared to Restasis® (cyclosporine ophthalmic emulsion 0.05%) for the treatment of dry eye syndrome (DES). Though similar in structure and binding affinity, voclosporin has an additional single carbon extension with a double-bond on one side chain compared to cyclosporine. Upon binding, the ethynyl side chain of voclosporin induces structural changes that may result in increased immunosuppressive activity compared to cyclosporine.

On secondary endpoints, including Schirmer Tear Test and fluorescein corneal staining, VOS showed rapid and statistically significant improvements over Restasis® at week four (STT: $p=.0051$; FCS: $p=.0003$), while both groups saw substantial and significant improvements on the Symptom Assessment in Dry Eye when comparing baseline measures to results at week four. Notably, 42.9% of VOS-treated patients demonstrated a ≥ 10 mm improvement in Schirmer Tear Test scores at week four compared to 18.4% of patients receiving Restasis® ($p=.0055$). It is important to note that no statistical difference was seen on the primary endpoint, drop discomfort at one-minute post-dose one installation, as both treatments exhibited low drop discomfort scores. This double masked, head-to-head study included 100 patients who received twice daily treatment in both eyes for a period of 28 days. An Aurinia spokesperson has stated that based on this data, they plan to aggressively advance VOS for the treatment of DES.

Merger Announced Between Quest and OraHealth

Quest Products, Inc., a portfolio company of Promus Equity Partners, announced a merger with Orahealth Corporation, Inc. This merger will bring the Oracoat® brand of oral care products as well as Xylimelts® for dry mouth to Quest.

BMS and Celgene Announce One of the Largest Pharma Merges in History

Bristol-Myers Squibb (BMS) has agreed to acquire Celgene for \$74 billion cash-and-stock, uniting the two companies in one of the largest pharmaceutical company mergers in history. As a result of this deal, BMS will gain control of Revlimid, one of the most successful cancer drugs on the market, as well as promising therapies being developed by Juno Therapeutics, which was acquired by Celgene in 2018. Giovanni Caforio, M.D., Chairman and Chief Executive Officer of Bristol-Myers Squibb, was optimistic about what the future of this merger would hold, noting the enhancement of their leadership positions across their portfolio, including immunology and inflammation and their ability to accelerate new options through a broader range of cutting-edge technologies and discovery platforms.

Kala's NDA for DE Treatment Accepted

The U.S. FDA has accepted a new drug application submitted by Kala Pharmaceuticals for their drug KPI-121 0.25%, a topical treatment for dry eye disease. The drug uses Kala's AMPPLIFY mucus-penetrating particle drug delivery technology to target delivery of lotepred-nol etabonate to ocular tissues. KPI-121 0.25% would be the first FDA-approved product for the temporary relief of dry eye signs and symptoms.

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to controls ($p < 0.01$). Additionally, the density of the inner layer of wing cells was decreased in both the non-Sjögren's dry eye ($P < 0.05$) and Sjögren's dry eye ($P < 0.01$) groups when compared to controls.

Citation

Lee OL et al. Evaluation of the corneal epithelium in non-Sjögren's and Sjögren's dry eyes: an in vivo confocal microscopy study using HRT III RCM. *BMC Ophthalmol.* 2018 Dec 4;18(1):309. doi: 10.1186/s12886-018-0971-3.

Meibomian Gland Morphology as an Early Indicator of MGD

Morphologic analysis of the Meibomian glands helps reveal early stage meibomian gland dysfunction (MGD) and represents a complementary clinical parameter with diagnostic potential. Investigators graded, on a scale of 0 to 3, the meibomian gland loss on meibography images of the upper (UL) and lower lids (LL) and found that MGD patients had significantly higher meibogrades for both lids ($p < 0.001$ for UL and LL). Schirmer's values were significantly increased in MGD patients with meibograde 1 compared to the other groups ($p < 0.05$) and MG thickness increased in-line with higher meibogrades ($p < 0.001$). The MG morphology correlated with several clinical parameters, though OSDI did not correlate with any morphological parameter. The sensitivity and specificity of the meibograde as a diagnostic parameter for MGD was 96.7% and 85%, respectively. This cross-sectional study included 538 MGD patients and 21 healthy controls.

Citation

Adil MY et al. Meibomian gland morphology is a sensitive early indicator of meibomian gland dysfunction. *Am J Ophthalmol.* 2018 Dec 19. pii: S0002-9394(18)30675-5. doi: 10.1016/j.ajo.2018.12.006. [Epub ahead of print]



Clinical News: Oral

Efficacy of Xerostom® on Dry Mouth in Sjögren's Patients

Xerostom® mouthwash and toothpaste may help to alleviate side effects of xerostomia in Sjögren's patients and improve quality of life, but researchers feel that additional efficacy studies with larger groups of patients are needed. For this study, Sjögren's patients were placed in test ($n=13$) and control ($n=11$) groups and used the given products three times per day for 28 days. Visual analogue scores for xerostomia and the Oral Health Impact Profile-14 (OHIP-14) were used at baseline and after treatment. Importantly, significant improvements in OHIP-14 were noted in the treatment group.

Citation

Lopez-Pintor RM et al. Effects of Xerostom® products on xerostomia in primary Sjögren's syndrome: a randomised clinical trial. *Oral Dis.* 2018 Dec 17. doi: 10.1111/odi.13019. [Epub ahead of print]

Correlations Between Hyposalivation Tests and Dry Mouth Measurement Scales

Investigators have found significant correlations between xerostomia scoring systems and a variety of hyposalivation measures in a study of Sjögren's patients ($n=49$). Specifically, the Clinical Oral Dryness Scale (CODS) showed a significant correlation with stimulated whole saliva flow ($P=0.048$) and stimulated parotid flow ($P=0.009$). The dryness domain of ESSPRI was found to be significantly correlated with unstimulated whole saliva flow ($P=0.031$), and, notably, the Xerostomia Index was not found to be correlated with any of the investigated measures of hyposalivation.

Citation

Hijaw O et al. Correlation between Xerostomia index, Clinical Oral Dryness Scale, and ESSPRI with different hyposalivation tests. *Open Access Rheumatol.* 2019 Jan 4;11:11-18. doi: 10.2147/OARRR.S188937. eCollection 2019.

"Industry News" Continued from page 15 ▼

First Biosimilar for Rituxan Approved by FDA

Celltrion Inc. has received U.S. FDA approval for Truxima, a biosimilar to Roche's Rituxan, for the treatment of non-Hodgkin's lymphoma. As noted in Vol. 13, Issue 3 of *Sjögren's Quarterly*, the FDA had previously rejected multiple Celltrion biosimilars, including Truxima, in Spring 2018, citing manufacturing concerns. Celltrion will market the drug in the U.S. in partnership with Teva Pharmaceutical Industries.

Alcon Acquires Manufacturers of iLux® Device

Alcon, a division of Novartis, has announced its acquisition of Tear Film Innovations, Inc., the manufacturer of the iLux® Device, a therapeutic device used to treat meibomian gland dysfunction. This acquisition expands Alcon's portfolio of ocular health products, which includes several leading treatments for the temporary relief of dry eye symptoms.

New Dry Mouth Spray Released by 3M

3M has launched a professional-grade solution designed to provide rapid, effective and convenient relief of xerostomia symptoms. This lipid based solution utilizes oxygenated glycerol trimester technology and creates a protective lipid film consisting of oxidized glycerol triesters, silicon dioxide, sugar-free sweetener and flavoring. The spray is available by prescription only and is indicated to last for up to four hours per use.

SSF In Action



SSF's Hammitt Appointed to NIH Pain Committee

Katherine Hammitt, Vice President of Medical and Scientific Affairs at the SSF, has been nominated and appointed to serve on the Interagency Pain Research Coordinating Committee for a two-year term, ending in 2020. By law, the committee was formed and tasked with the following duties: to develop a summary of advances in pain care research supported or conducted by the Federal agencies relevant to the diagnosis, prevention, and treatment of pain and diseases and disorders associated with pain; identify critical gaps in basic and clinical research on the symptoms and causes of pain; make recommendations to ensure that the activities of the National Institutes of Health and other Federal agencies are free of unnecessary duplication of effort; make recommendations on how best to disseminate information on pain care; and make recommendations on how to expand partnerships between public and private entities to expand collaborative, cross-cutting research.

SSF Participates in a Variety of Fall NHC Meetings

From October through December, SSF staff participated in a number of meetings organized by the National Health Council (NHC). In October, Matt Makara, Director of Research and Scientific Affairs at the SSF, participated in the Chief Medical and Scientific Officers Conference, where leaders from across sectors and an array of attendees discussed ideas and best practices for engaging patients for clinical research, using and sharing data and more. In November, Makara participated in the meeting of Washington-based representatives to discuss the NHC's advocacy and legislative focus for 2019. Lastly, in December, Steven Taylor, SSF CEO, and Ben Basloe, Vice President of Philanthropy at the SSF, attended the 2018 Annual Membership Meeting and Luncheon in Washington, DC. Here, Marc Boutin, CEO of the NHC, provided a report on the year, new and outgoing members were recognized and nominations for the 2019-2021 Board were approved.

SSF's Hammitt Participates in SG's Listening Session on Oral Health

Katherine Hammitt, Vice President of Medical & Scientific Affairs at the SSF, participated in the U.S. Surgeon General's Oral Health Listening Session on November 26th, 2018, to help inform a new report, *Oral Health in American: A Report of the Surgeon General*. A key theme of the event was oral health as an integral factor to overall health and how primary care physicians and dentists need to collaborate to ensure better patient outcomes. The new report, the first in nearly 20 years, will document the progress made over the past two decades, identify current knowledge gaps and articulate a vision for the future. This initiative is headed by the U.S. Department of Health and Human Services, the Office of the Surgeon General, the NIH, the NIDCR and the U.S. Public Health Service Oral Health Coordinating Committee. Hammitt attended the session as a representative of the special care needs for the Friends of the National Institute of Dental and Craniofacial Research (FNIDCR) Patient Advisory Council and the Sjögren's community. ■

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. 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.

"Industry News" Continued from page 16 ▼

LO2A Meets Primary Objective in Phase II Trial

Israel-based Wize Pharma, Inc., announced top line results from its Phase II clinical trial of LO2A for the symptomatic treatment of dry eye syndrome in patients with moderate-to-severe conjunctivochalasis. This multicenter, randomized, double-blind, placebo-controlled study had a primary endpoint of a reduction in lissamine green conjunctival staining score from baseline to three months. A mixed model with repeated measures utilizing all post-baseline observations demonstrated statistical significance between the LO2A and placebo group ($p=0.0079$). Additionally, the average reduction in lissamine green conjunctival staining score from baseline to three months demonstrated a strong trend towards significance ($p=0.0713$) with an average reduction in scores between baseline and three months of -3.5 (LO2A) and -1.6 (placebo).

NOV03 Improves Corneal Staining in Phase II Trial

NOV03, a preservative-free ophthalmic solution, met

its primary endpoint in a Phase II clinical trial for the improvement of total corneal fluorescein staining compared to controls at eight weeks. The trial included two dosage groups, both of which showed effects as early as two weeks into the study, which were maintained throughout the study period. NOV03 is a product under development by Novaliq.

Positive Results for CyclASol® in Phase IIb/III Trial

Novaliq has shared that CyclASol®, a preservative-free ophthalmic solution of 0.1% cyclosporine A in EyeSol®, the first water-free technology for ophthalmology, has met the primary efficacy endpoint in the ESSENCE Phase IIb/III clinical trial. The primary efficacy endpoint being evaluated was total corneal fluorescein staining over vehicle at four weeks, which showed high statistical improvement when comparing the treatment vs vehicle groups ($p=0.0002$). Ocular Surface Disease Index scores, a second primary endpoint, indicated that all patients involved in the study benefited from the treatment. ■

In Memory of Stephen Katz, MD, PhD



Stephen I. Katz, MD, PhD, 1941 – 2018

The Sjögren's Syndrome Foundation joins with the National Institutes of Health and others in mourning the loss of Dr. Stephen Katz.

Dr. Katz graduated from the Tulane University Medical School with honors in 1966. He completed a medical internship at Los Angeles County Hospital and did his dermatology residency at the University of Miami Medical Center from 1967 to 1970. He served in the U.S. military at Walter Reed Army Medical Center from 1970 to 1972. From 1972 to 1974, Dr. Katz did a postdoctoral fellowship at the Royal College of Surgeons of England and obtained a PhD degree in immunology from the University of London in 1974.

He then became Senior Investigator in the Dermatology Branch of the National Cancer Institute (1974-2014) and assumed the position of Acting Chief in 1977. In 1980, he became Chief of the Branch, a position he held until 2002. In 1989, Dr. Katz also assumed the position of Marion B. Sulzberger Professor of Dermatology at the Uniformed Services University of the Health Sciences in Bethesda,

Maryland, a position that he held until 1995.

Dr. Katz served as Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases between August 1995 up until the time of his passing. During this time, he also served as an Adjunct Investigator in the Dermatology Branch of the National Cancer Institute.

In his remembrance, Francis Collins, NIH Director, had this to say about Dr. Katz's contributions and impact, "But I would claim that there is no Institute Director who has done more over the last two decades to help the entire NIH enterprise flourish... May we strive to live up to the example of dedication and wisdom set by our dear friend Steve."

He will be remembered as an outstanding scientist, administrator, and civil servant who was committed to excellence, transparency, integrity, and public trust. ■



Patient Education Sheet

Health Insurance Tips – Part 1

Obtaining healthcare reimbursement can be a major challenge. Having Sjögren's places a high enough burden on patients, and adding the barriers patients face in obtaining health insurance reimbursement increases that burden greatly. This tip sheet should help you increase your chances of success when requesting reimbursement and appealing denials for a claim.

Know your insurance policy and what it covers.

- Note whether prior authorization is needed for a specific therapy or procedure.
- Understand co-pays and how much you will be expected to contribute to the cost.
- Know whether your insurance company requires "step therapy," which means you must try and fail one therapy before the next level of therapy can be covered.
- Make sure your medical records are accurate.
- Maintain copies of your medical records. You have the right to receive copies of all of your medical records. Note that you can be charged a copy fee.
- Include a Letter of Medical Necessity.
- A Letter of Medical Necessity is usually written by the physician explaining why a therapy or other treatment is medically necessary. This can be included with an initial claim or included in the appeals process.
- A sample Letter of Medical Necessity for dental treatment can be found on the SSF website under "Brochures and Resource Sheets."
- Know how your insurance company handles biologics if you are considering one.
- Insurance companies can exclude a drug from coverage or it might be a "tiered" drug, meaning one that is designated at a certain level for how much the patient must cover.
- If not covered, or if the patient coverage is too high, request an exemption along with an explanation about why you need the drug from your physician.
- Always appeal denials!
- Appeal a denial at every level. Most patients receive at least partial reimbursement upon appealing a negative decision from their insurance company.
- Involve your doctor in helping you respond to a denial.
- Familiarize yourself with your insurance company's guidelines and deadlines for appeal. This information is usually included in the denial letter.
- Make sure you have the necessary documentation showing that your case meets the insurance provider's guidelines and demonstrates medical need.
- Maintain records of your communication with the insurance company and document every time you speak or hear from a company representative. Record the person's name, date, time and key messages from the conversation.
- Understand why you were denied, so you can address the reason(s) directly.
- If you are communicating with the customer service office of the insurance company and are dissatisfied with the response, ask for a nurse case manager or a supervisor who might be more understanding of your situation.
- When possible, demonstrate that treatment is more cost-effective than alternatives or non-treatment.
- If you are still denied following the final round of appeals, contact the advocacy or patient assistance program for the company that produces the therapy. Most companies have divisions that take applications for financial assistance for their therapies.

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

SSF's Taylor Nominated as Chair of NHC Board of Directors

Steven Taylor, SSF CEO, will serve as Chair of the National Health Council (NHC) Board of Directors in 2019. As an organization, the NHC brings together all segments of the health community to provide a united voice for the more than 160 million people with chronic diseases and disabilities as well as their families and caregivers. NHC members include more than 125 national health-related organization, including the SSF, who's involvement helps to further the recognition of Sjögren's while elevating our voice and ensuring that we participate in discussions and decisions important to the Sjögren's community.

Taylor will be joined by the following esteemed leaders as part of the NHC 2019 Executive Committee and Board of Directors:



Steven Taylor (right) and Robert Gebbia (left) at the 2018 NHC Annual Membership Meeting. Photo credit: National Health Council

2019 Executive Committee

*Chair: Steven Taylor,
Chief Executive Officer, Sjögren's Syndrome Foundation*

*Chairperson-Elect: Ann Palmer,
President & Chief Executive Officer, Arthritis Foundation*

*Vice Chairperson: Gary Reedy,
Chief Executive Officer, American Cancer Society*

*Secretary: Matt Eyles,
President & Chief Executive Officer,
America's Health Insurance Plans*

*Treasurer: Cassandra McCullough,
Chief Executive Officer, Association of Black Cardiologists*

*Immediate Past Chairperson: Robert Gebbia,
Chief Executive Officer, American Foundation
for Suicide Prevention*

2019 Board of Directors

*Nancy Brown, Chief Executive Officer,
American Heart Association*

*Stevan Gibson, President & Chief Executive Officer,
Lupus Foundation of America;*

*Eyles McCullough; Harold "Hal" Paz,
Executive Vice President and Chief Medical Officer, Aetna;*

Sue Sherman, Executive Director, The LAM Foundation;

*Tracey Brown, Chief Executive Officer,
American Diabetes Association;*

*LaVarne Burton, President & Chief Executive Officer,
American Kidney Fund;*

*Chip Davis, President & Chief Executive Officer,
Association for Accessible Medicines;*

*Elizabeth Fowler, Vice President,
Global Health Policy, Johnson & Johnson;*

*Patricia Furlong, Founding President and CEO,
Parent Project Muscular Dystrophy;*

*Diana Gray, Chief Executive Officer,
Hydrocephalus Association;*

*Dory Kranz, Chief Executive Officer,
National Alopecia Areata Foundation;*

Richard Pops, Chief Executive Officer, Alkermes;

*Lisa Simpson, President & Chief Executive Officer,
AcademyHealth; and*

Stephen Ubl, President & Chief Executive Officer, PhRMA.