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Is Stress a Major Player in the Pathogenesis of Sjögren's Syndrome?

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Stress and autoimmunity

A large body of clinical studies support the association between stressful life events and autoimmunity. Physical and emotional stresses are major environmental factors with underestimated impact on the disease development.[1-2] During the last decades, studies on psychoneuroimmunology and immune-endocrinology have focused on the mechanisms through which stress affects the immune system.

Psychological stress, as well as the mechanisms involved to cope with it, activate hormonal circuits. The two main stress-induced hormonal responses are the hypothalamic-pituitary-adrenal (HPA) axis and the Autonomic Nervous System (ANS). Inadequate secretion of cortisol as well as increased sympathetic tone at rest but an inadequate response during stress exposure seem to be key factors for stress-induced aggravation of chronic inflammatory rheumatic

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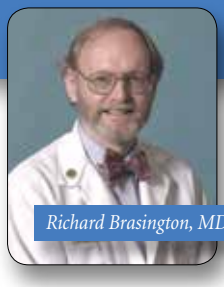
Clinician's Corner

Vaccinations in Sjögren's Syndrome



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One of the most important aspects of "preventive health care" is receiving the appropriate vaccinations. This is particularly important for patients with autoimmune disease with comprised immune function, especially when immunosuppressive medications are used. We can think of vaccinations in three broad categories: 1) those which everyone should receive; 2) those which are particularly appropriate for patients with autoimmune diseases; and 3) vaccines which may be dangerous for such patients and therefore should be avoided.

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diseases. These findings, however, cannot directly support the notion that stress may be the initiator of autoimmune reaction and development of autoimmune disease.

In a recent article we supported the hypothesis that chronic stress holds a triggering role in autoimmune reactivity, not only through its effect on the immune system but through its effects on the tissues against which the autoreactivity is expressed.[3]

Stressful life events, chronic stress and Sjögren's patients

Sjögren's syndrome is an ideal prototype of disease for the study of the effects of stress on autoimmune reactivity and disease development for the following reasons: 1) the disease development process runs a slow course; 2) the affected individuals are rather homogeneous since patient's sex, hormonal status and age are similar; 3) the disease process does not raise a systemic inflammatory response, which can alter the body's psycho-endocrine homeostasis; 4) the majority of patients do not receive immunosuppressive agents which could potentially interfere with immune cell populations and functions; and 5) the histopathologic lesion in the minor labial salivary glands is easily accessible without any risk of morbidity.

Clinical observations in Sjögren's patients have shown that negative stressful life events, like loss of loved ones, divorce, economic catastrophe and other undesirable conditions precede the development and/or the exacerbation of the disease.[4] Furthermore, analysis of patients' personality traits and psychosocial status has shown an inability to cope and handle stressful situations, a personality characterized by hypochondriasis, neuroticism, and obsessiveness and expression of high levels of introverted hostility.[5-6]

Two decades ago, the response of the HPA axis was evaluated in Sjögren's.[7] Although patients with Sjögren's responded to Corticotrophin-Releasing Hormone (CRH) administration with an increase in corticotrophin (ACTH) and cortisol levels, their basal activity was low and associated with pituitary and adrenal hypo-responsiveness. These findings, at that time, were attributed to defective adrenal function. However, a newer study on patients with Sjögren's evaluating the adreno-medullary response to glucagon revealed that the patients' adreno-medullary function was comparable to that of healthy controls. Therefore, the low ACTH and cortisol response to CRH in Sjögren's patients appears to mimic the HPA pattern of response observed in individuals under chronic stress.[8]

Chronic stress is also characterized by derangement of the responses of ANS to stressors. In response to mild stressors the ANS activates the sympathetic system, which is accompanied by a reciprocal decrease of parasympathetic tone. Subsequently, sympathetic activation diminishes, parasympathetic tone returns to normal, and the whole system resets to physiological function.

If a stressor is above certain intensity or duration, the sympathetic response is more intense. If the response is inadequate, the system as a whole may fail to reset to a normal level of functionality, remain "tuned" to excess sympathetic and deficient parasympathetic activation, and the ANS does not reset to baseline status. This condition may persist indefinitely, giving rise to a state of "chronic stress" where the ANS responds inappropriately to environmental challenges with an excessive activation.[9] The HPA and ANS responses to stressors show marked differences according to sex, phase of the menstrual cycle, menopausal status and pregnancy. During the luteal phase the HPA axis response is higher, while after menopause there is an increase in sympatho-adrenal responsiveness.[10]

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Erratum

Sjögren's Syndrome and Gut Bacteria – What's the Connection?

Sjögren's Quarterly, Winter, 2018

Anat Galor, MD, MSPH; Santanu Banerjee, PhD; Kara M. Cavuoto, MD

Reference number 15 in the original article was listed incorrectly. The correct reference is as follows:

15. De Paiva CS, Jones DB, Stern ME, Bian F, Moore QL, Corbiere S, Streckfus CF, Hutchinson DS, Ajami NJ, Petrosino JF, Pflugfelder SC. Altered mucosal microbiome diversity and disease severity in Sjögren syndrome. *Sci Rep*. 2016; 6: 23561 ■

In the case of Sjögren's, the majority of the patients are mainly menopausal women, who have experienced stressful incidents in their lives and their HPA axis response resembles that of individuals in chronic stress. Thus, the ANS of these patients, following the irregular HPA response, may be in a constant imbalance, characterized by high sympathetic and low parasympathetic tone.

Stress and salivary gland epithelial cells

The chronic imbalance of sympathetic and parasympathetic activity has a severe impact on tissues, the function of which is closely dependent on ANS. The salivary and lachrymal gland functions are inherent with ANS. The stimulation of saliva production is mediated through taste and mastication and depends largely on the ANS. Protein secretion is exclusively controlled by noradrenaline through β-adrenergic stimulation, while the watery component of saliva is regulated by signals from the parasympathetic nervous system through the action of acetylcholine (ACh) on the muscarinic receptors.

In addition to stimuli for food digestion, the salivary glands concurrently receive signals from ANS in response to stress. The decrease of parasympathetic tone leads to decreased watery component of saliva, while the increase of catecholamine levels results in an increased concentration of saliva proteins. These responses led the investigators to study saliva amylase levels as an indicator of adrenergic activity in different types of stressors. Saliva amylase levels increase in normal individuals after a stressful event, while its levels do not change in persons under chronic stress, who receive a similar stress load. We postulate that a constantly high sympathetic and low parasympathetic status of the body results in metabolic stress of the salivary gland epithelial cells, leading to low saliva flow and inadequate quantity and quality of saliva proteins. Thus, chronic stress seems to lead to an ineffective coordination of the mechanisms involved in protein synthesis and secretion, leading the endoplasmic reticulum to a constant stress status, which can finally give signals directing the salivary epithelial cell to apoptotic death.

The endoplasmic reticulum is a net like labyrinth of branching tubules and flattened sacs extending in the cells' cytoplasm and its main function is the production, processing and transport of proteins inside the cell. Although a series of cellular mechanisms are upregulated to reverse metabolic stress, apoptotic death is often the final step of this process. Apoptosis is a silent way of cell death and under physiological conditions does not evoke immunogenic reactions. However, when apoptosis is the result of intense stress to the endoplasmic reticulum, apoptotic cells become immunogenic by expressing endogenous autoantigens.

During the last 20 years in the attempt to understand the pathogenesis of Sjögren's, histopathology of salivary gland lesion and cell culture studies have shown that immune-related molecules were inappropriately expressed by ductal and acinar epithelial cells of Sjögren's patients, while accelerated apoptosis was detected which was not related to the inflammatory load.[11-12]

We recently have shown that during apoptosis of salivary gland epithelial cells following endoplasmic reticulum stress, autoantigens Ro/SSA and La/SSB were detected in the apoptotic blebs of these cells.[13] Animal studies also support the notion that endoplasmic reticulum stress of the salivary gland cells led them to immunogenic apoptosis.[14]

Immunogenic apoptosis is the final mechanism by which the stressed salivary gland epithelial cells trigger the immune system specifically. However, during the cell's struggle to support its function and survival, additional components are upregulated and recognized as potential inducers of inflammatory and immune response. In fact, upregulation of certain genes of the glandular epithelial cells lead to production of interferon and interleukin-6 molecules as well as expression of MHC II molecules on their surface, rendering them able to orchestrate the autoimmune reactivity observed in the diseased tissues of Sjögren's.

In brief, our proposed hypothesis is the following:

The patients that will develop Sjögren's have stressful events in their life that they cannot handle properly and live under chronic stress. In menopausal women, as the majority of Sjögren's women, a new stressful event can be more rigorous.

Chronic stress leads to an excess sympathetic and deficient parasympathetic activation. This imbalance leads to chronic metabolic dysfunction of the salivary glands leading them to a chronic struggle for survival. The response to new stress, under these conditions, may not be efficient, leading the cells to apoptosis.

As a result of apoptosis, translocation of cellular antigens such as Ro/SSA ribonucleoprotein and chaperon proteins occurs. This leads to a specific autoimmune reaction in a milieu of cytokines/chemokines, which has been prepared by a preceding innate immune activation during the endoplasmic reticulum stress process. New cytokines are up regulated and the immune injury perpetuates.

Our research program at Harokopio University, Athens, Greece, aims at dissecting, at the molecular level, the impact of stress on the metabolic status of salivary gland epithelial cells and their transformation to immunogenic cells. Our research efforts are guided by the argument that stress through the salivary gland

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"Stress…" Continued from page 3 ▼

epithelial cell plays a crucial role in the pathogenesis of Sjögren's, since these cells are the common targets of stress as well as the autoimmune injury. The outcome of this research would form the foundation for testing the potential therapeutic value of stress and/or metabolic cell stress-targeting in preventing Sjögren's. ■

References

1. Porcelli B, Pozza A, Bizzaro N, Fagiolini A, Constantini MC, Terzuoli L, Ferretti F. Association between stressful life events and autoimmune diseases: A systematic review and meta-analysis of retrospective case-control studies. *Autoimmunity Reviews 2016*; 15:325-334.
2. Kemeny ME, Schedlowski M. Understanding the interaction between psychosocial stress and immune-related diseases: A stepwise progression. *Brain, Behavior and Immunity* 2007; 21: 1009-1018.
3. Skopouli FN, Katsiougiannis S. How stress contributes to autoimmunity-lessons from Sjögren's syndrome. *FEBS Lett*. 2018; 592:5-14.
4. Karaiskos D, Mavragani CP, Makaroni S, Zinzaras E, Voulgarelis M, Rabavilas A, Moutsopoulos HM: Stress, coping strategies and social support in patients with primary Sjögren's syndrome prior to disease onset: a retrospective case-control study. *Ann Rheum Dis* 2009; 68:40-46.
5. Drosos AA, Angelopoulos NV, Liakos A, Moutsopoulos HM. Personality structure disturbances and psychiatric manifestations in primary Sjögren's syndrome. *J Autoimmun*. 1989; 2:489-493.
6. Karaiskos D, Mavragani CP, Hamze Sinno M, De´chelotte P, Zintzaras E, Skopouli FN, Fetissov SO and Moutsopoulos HM. Psychopathological and personality features in primary Sjögren's syndrome—associations with autoantibodies to neuropeptides. *Rheumatology* 2010; 49:1762–1769.
7. Johnson E, Skopouli FN, Moutsopoulos HM. Neuroendocrine manifestations in Sjögren's syndrome. *Rheumatic Disease Clinics of North America* 2000; 26:927-949.
8. Minton JE. Function of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system in models of acute stress in domestic farm animals. *J Anim Sci* 1994; 72:1891-1898.
9. Payne P, Levine PA and Crane-Godreau MA. Somatic experiencing: using interoception and proprioception as core elements of trauma therapy. *Front Psychol*. 2015; 6:93-102.
10. Kajantie E, Philips DIW: The effects of sex and hormonal status on the physiological response to acute psychosocial stress. *Psychoneuroendocrinology* 2006; 31: 151-178.
11. Moutsopoulos HM. Sjögren's syndrome: autoimmune epithelitis. *Clin Immunol Immunopathol* 1994; 72:162–165.
12. Polihronis M, Tapinos NI, Theocharis SE, Economou A, Kittas C, Moutsopoulos HM. Modes of epithelial cell death and repair in Sjögen's syndrome. *Clin Exp Immunol* 1998; 114:485-490.
13. Katsiougiannis S, Tenta R and Skopouli FN. Endoplasmic reticulum stress causes autophagy and apoptosis leading to cellular redistribution of the autoantigens Ro/ Sjögren's syndrome -related antigen A (SSA) and La/SSB in salivary gland epithelial cells. *Clin Exp Immunol* 2015; 181:244-252.
14. Okuma A, Hoshino K, Ohba T, *et al*. Enhanced apoptosis by disruption of the STAT3-IjB-f signaling pathway in epithelial cells induces Sjögren's syndrome-like autoimmune disease. *Immunity* 2013; 38:450-460.

"Vaccinations…" Continued from page 1 ▼

Updating vaccinations is particularly important before receiving some immunosuppressive medications, because these can seriously blunt a person's response to appropriate vaccination.

Nowadays, the "standard" vaccinations are administered during the pre-school and elementary school years and include mumps, measles, rubella, tetanus, diphtheria, etc. For purposes of this discussion, we will assume that all patients who are ultimately diagnosed with Sjögren's have received all of the appropriate childhood immunizations. All adults need to remember that at least every ten years they should receive a tetanus and diphtheria "booster." In reality, this booster is often administered when a question arises as to whether tetanus immunity is current; if there is no documentation of a Td booster in the previous ten years, it is given at that point.

Note that the Varicella vaccine is a live virus vaccine, and should not be given to immunosuppressed persons.

Patients with autoimmune disorders such as Sjögren's are generally considered to have some compromise of the immune system and increased susceptibility to infection. A simple way to think of this is to consider that if the immune system is "misdirected" toward self, it probably is not doing an ideal job of protecting against infectious agents. Obviously, someone with mild Sjögren's who does not have pronounced systemic disease will not be as susceptible to infection as a patient with systemic disease requiring prednisone and/or immunosuppressive agents such as azathioprine, methotrexate, mycophenylate mofetil, rituximab, or cyclophosphamide. Nonetheless, I recommend that all patients with Sjögren's undergo vaccination for influenza, pneumococcal pneumonia, and shingles.

While some patients fear that vaccines can activate the immune system and cause systemic flares, no scientific evidence exists to indicate that this is the case. In fact studies in systemic lupus erythematosus (SLE) do not suggest disease activation with Pneumovax®. Vaccines need only be avoided when a previous reaction has occurred, and a reaction to one vaccination does not mean that all future vaccinations should be avoided.

The annual "flu shot" each fall is familiar to everyone. This vaccine is different each year and must be given every year. The vaccine for a given flu season is developed based on scientists' best predictions of which strains of influenza virus will be dominant that particular year. Hence, immunity one year does not necessarily carry over until the next year. Even when vaccination does not prevent the occurrence of influenza in those vaccinated, it is likely that the illness will not be as severe in those vaccinated.

The "pneumonia shot" (Pneumovax®, or pheumoccal polysaccharide vaccine) specifically protects against one kind of bacterial pneumonia, pneumococcal pneumonia, and covers twenty-three serotypes. Those who are elderly or chronically ill are particularly at risk of developing severe, even fatal, pneumococcal infections.

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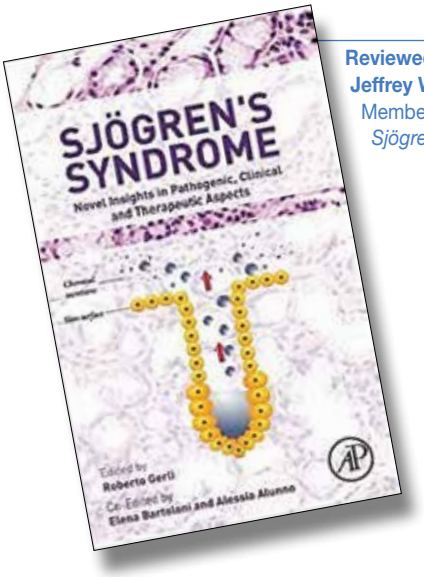
Recommended Reading: Expert Book Reviews

Sjögren's Syndrome: Novel Insights in Pathogenic, Clinical, and Therapeutic Aspects

Edited by Roberto Gerli; Co-edited by Elena Bartolini and Alessia Alunno



Reviewed by
Jeffrey W. Wilson, MD, FACR
Member, SSF Medical & Scientific Advisory Board, At-Large Medical and Scientific Editor and Reviewer, *Sjögren's Quarterly*, Retired, Rheumatology practice, Lynchburg, VA

Sjögren's Syndrome: Novel Insights in Pathogenic, Clinical, and Therapeutic Aspects (Elsevier Academic Press 2016; edited by Roberto Gerli; co-edited by Elena Bartoloni and Alessia Alunno) is presented as "a comprehensive and exhaustive overview of current knowledge on Sjögren's Syndrome and provides the most up-to-date information available on the disorder."

In 324 pages the 45 contributors provide a complete review of past areas of investigation, current research, plus future directions for Sjögren's studies. The first six chapters relate the history of Sjögren's, clinical manifestations, diagnostic and therapeutic modalities.

The next 14 chapters will be of great interest and value to academic research oriented basic scientists and most clinicians. They serve as a bridge between the clinical aspects and the basic science related to Sjögren's. Each chapter is followed by an abundance of relevant references. A complete five and a half page index completes the book.

Figures and tables enhance and clarify the text throughout. Witness this in Chapter 5 on imaging procedures and in Table 9.2 Association Between Autoantibodies Expression and Clinical Features, which supports consideration of the pathogenicity of autoantibodies.

One model for the development of autoimmune diseases like Sjögren's is the idea of a setting (inherited tendency, epigenetics, vitamin D insufficiency), exposure to a trigger (infectious, environmental), and subsequent activity of autoimmune processes. In chapters 8 through 16 the contributors present current information and past, plus ongoing, research in these areas (epithelial cell, B cells, T cells, cytokines, chemokines). With limitations of the mouse research model (Chapter 7), chapters 17 through 20 deal with clinical trial design and outcome measures, treatment strategies targeted specifically to B cells and T cells, and the future potential of biomarkers allowing stratification of Sjögren's patients and personalized therapy.

Another book, *Sjögren's Syndrome* (edited by Wan-Fai Ng), was also published in 2016. Gerli's and Ng's works complement each other. This is not surprising since some contributors (Francesca Barone, Simon Bowman, Serena Colafrancesco, and Benjamin Fisher) appear in both works. Ng's book, as intended, serves as more of a ready referral pocketbook for clinical information and treatment guidelines. Gerli's book provides a more comprehensive understanding of basic science and research pursuits.

Both books are recommended for those interested in Sjögren's at any level. Gerli's book achieves the goal proposed initially: "a comprehensive and exhaustive overview of current knowledge on Sjögren's Syndrome." ■

If you have recommendations for books that you'd like to see reviewed, please contact Matt Makara at mmakara@sjogrens.org.

"Vaccinations…" Continued from page 4 ▼

For some persons, a second dose is recommended.

There has been an important advance in vaccination against pheumococcal pneumonia with the advent of Prevnar®, or Pneumococcal 13-valent Conjugate Vaccine. Prevnar® provides additional protection, and should also be given. The order in which one receives Pneumovax® and Prevnar® depends upon a number of issues, so you should consult with your physician about this. Everyone with Sjögren's should receive these vaccines, unless there are specific medical reasons to the contrary.

The third category of vaccines to consider is the "live virus" vaccines. The vaccines discussed above are made of killed viruses or bacteria and pose no risk of infection. However, vaccination with a live virus does pose some risk of infection, and in someone with an autoimmune disease on immunosuppressive medication, this may be quite dangerous. One such live attenuated vaccine is FluMist®, which is administered as a nasal spray. FluMist® should not be given to immunosuppressed patients. The definition of immunosuppressed is open to interpretation but clearly includes patients taking prednisone or immunosuppressive agents such as azathioprine, methotrexate, cyclophosphamide, rituximab, or mycophenylate mofetil.

There has been a major new development in the "shingles vaccine." Zostavax is an attenuated live virus vaccine which cannot safely be administered to patients who are significantly immunosuppressed. The new vaccine, Shingrix (recombinant zoster vaccine), is a "killed virus" vaccine, and therefore is not as risky to immunosuppressed persons. Furthermore, it appears that it is much more effective than Zostavax in preventing shingles. The Centers for Disease Control recommends Shingrix over Zostavax, and recommends two doses separated by two to six months in "immunocompetent persons" 50 years of age and older, including patients on "low dose immunosuppression." This latter term is open to interpretation, so ask your doctor which vaccination is right for you.

Gardasil® protects against human papilloma virus infection and the complication of cervical cancer. Experience with this vaccine in young women with Sjögren's is limited; there is too little evidence to recommend its routine use.

For patients on chronic steroids, keep in mind that doses of prednisone higher than 30mg a day may alter antibody production. Ideally, vaccines should be administered at the lowest possible steroid dose. For patients on Rituxan®, vaccines should be given at least three weeks before the infusion in order to optimize antibody production. Similarly, vaccines should be given prior to a course of Cytoxan®, which can also suppress B lymphocyte function. IVIg should not pose a problem and, in fact, may provide what is known as passive immunity to many microbes.

In conclusion, my recommendation is that all patients with Sjögren's should have the pneumococcal pneumonia vaccine, yearly influenza vaccine and a tetanus-diphtheria booster at least every ten years. Vaccination against shingles is now less complicated, and should be strongly considered. Live virus vaccines such as Flumist® and Zostavax should be avoided except in special circumstances to be determined by the physician. ■

Clinical News: Rheumatology

Daily Living Priorities and Barriers Identified by Sjögren's Patients

A UK-based research team sought to identify key barriers and priorities for participation in daily living activities to help inform future interventions for Sjögren's patients. In all, a group of 231 participants provided input, including 121 Sjögren's patients, 43 adults living with a Sjögren's patient and 67 health care professionals. This group contributed 463 ideas, which resulted in 94 statements grouped into seven themed clusters, including: patient empowerment; symptoms; well-being; access and coordination of healthcare; knowledge and support; public awareness and support, and; family and friends. Of these seven themes, "patient empowerment" and "symptoms" were identified as priorities. These findings support the need for interventions that improve patient empowerment, general well-being, access to care, education and social support as important contributors to facilitate daily living activities.

Citation

Hackett KL, Deane KHO, Newton JL, Deary V, Bowman S, Rapley T, Ng WF. A mixed-methods study identifying key intervention targets to improve participation in daily living activities in primary Sjögren's syndrome patients. *Arthritis care Res (Hoboken)*. 2018 Feb. doi: 10.1002/acr.23536.

Increased Hospitalization Rates Seen in Sjögren's patients

Researchers have found that patients with Sjögren's had significantly higher hospitalization rates compared to the general population. This retrospective population-based cohort study identified Sjögren's patients and controls using records found between 1976 and 2015. Hospitalization records spanned 1995 to 2016. In all, 160 Sjögren's patients experiencing 385 hospitalizations and accounting for 1,592 person years of follow-up and 466 controls experiencing 899 hospitalizations and accounting for 4,660 person years of follow-up were identified. Specifically, increases in hospitalization rates were seen for endocrine, nutritional and metabolic diseases and immunity disorders (RR 1.82, 95% CI 1.08 to 2.98), musculoskeletal system and connective tissue diseases (RR 1.49, 95% CI 1.05 to 2.05) and injuries and poisoning (RR 1.46, 95% CI 1.01 to 2.06).

Citation

Maciel G, Servioli L, Nannini C, Berti A, Crowson CS, Achenbach SJ, Matteson EL, Cornec D. Hospitalisation rates among patients with primary Sjögren's syndrome: a population-based study, 1995-2016. *RMD Open 2018*; 4:e000575. doi: 10.1136/rmdopen-2017-000575

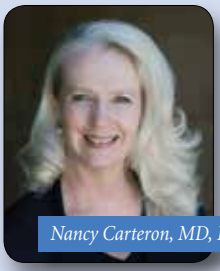
Epratuzumab shown more effective in SLE patients with Sjögren's than without

Findings from a post-hoc analyses of the EMBODY trials show that epratuzumab is more effective in patients with systemic lupus erythematosus (SLE) and Sjögren's than in patients with SLE alone. Study participants were divided into two groups: SLE patients with Sjögren's (n=113); and SLE patients without Sjögren's (n=1,375). Investigators found that, proportionally, a higher number of SLE patients with Sjögren's who received treatment with epratuzumab had a reduction from baseline in total BILAG score (British Isles Lupus Assessment Group), rapid clinical response to treatment composite score (BICLA), and a higher B cell sensitivity to epratuzumab – demonstrating a more rapid reduction in B cells, and a dose-dependent decrease in SSA antibodies. No differences in the frequency of side effects were noted between the groups.

Citation

Gottenberg JE, Dörner T, Bootsma H, Devauchelle-Pensec V, Bowman SJ, Mariette X, *et al*. Efficacy of epratuzumab, an anti-CD22 monoclonal IgG antibody, in systemic lupus erythematosus patients with associated Sjögren's syndrome: post-hoc analyses from the EMBODY trials. *Arthritis & Rheumatol*. Accepted Author Manuscript. doi:10.1002/art.40425

Commentary by Nancy Carteron, MD, FACR



Nancy Carteron, MD, FACR

B cells continue to be a probable therapeutic target in Sjögren's, despite a RCT that did not meet the primary clinical endpoint (TRACTISS). The epratuzumab post-hoc analyses also highlights the importance of further defining the clinical phenotype as we search for effective therapies in autoimmune disease.

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Ultrasound Used to Identify Enthesopathy in Sjögren's Patients

Researchers sought to determine the presence of enthesopathy by using the Madrid Sonographic Enthesitis Index (MASEI) in Sjögren's patients. In all, researchers evaluated 40 Sjögren's patients and 30 healthy controls by looking at six enthesis sites using gray-scale Doppler ultrasound with a linear transducer. Sjögren's patients were found to have significantly higher MASEI scores compared to the controls as well as significantly thicker plantar fascia, Achilles tendons and distal patellar tendons. The authors believe that this is both the first study to use an enthesis index ultrasonographically in Sjögren's patients as well as the first study to look into the relationship between enthesopathy and disease activity though ultrasound.

Citation

Sag S, Sag MS, Tekeoglu I, Kamanli A, Nas K. Presence of enthesopathy in patients with primary Sjögren's syndrome: ultrasonographic study of a local cohort. *J Med Ultrasonics* (2018). 45(1): 121-127

Rituximab Treatment Leads to Significant Improvement in TU Scores

Investigators in a multicenter, multi-observer, Phase III trial sub-study identified a significant improvement in total ultrasound score (TUS) after use with rituximab compared to placebo. Two groups of patients, one receiving rituximab (n=26) and one receiving a placebo (n=26), from nine centers were provided treatments at 0, 2, 24 and 26 week intervals with data being collected at baseline, 16 weeks and 48 weeks. Investigators analyzed the baseline-adjusted TUS scores over time to demonstrate change from baseline to each time point. Glandular definition improved in the rituximab arm with an OR of 6.8 (95% CI 1.1 to 43.0; P=0.043) at week 16 and 10.3 (95% CI 1.0 to 105.9; P=0.050) at week 48.

Citation

Fisher BA, Everett CC, Rout J, O'Dwyer JL, Emery P, Pitzalis C, *et al*. Effect of rituximab on a salivary gland ultrasound score in primary Sjögren's syndrome: results of the TRACTISS randomized double-blind multicenter study. *Annals of the Rheumatic Diseases*. 2018;77:412-416.

Analysis Finds RTX Ineffective in Sjögren's, but other Biologics Might Prove Beneficial

Investigators conducted a systematic literature review using MEDLINE, EMBASE and Cochrane for controlled or prospective studies on biological DMARDs modulating B cells in Sjögren's treatment with data on the effectiveness at 24 weeks related to fatigue, dryness, Schirmer test, salivary flow rate and full ESSDAI scores. In all, 18 articles were identified which met the inclusion criteria. Of these, 13 involved rituximab, three involved belimumab and one each for epratuzumab and baminercept, respectfully. No significant differences were noted between treatment with rituximab and a placebo, supporting that it is not effective in the treatment of Sjögren's based on the designs and outcomes identified in the studies. Additionally, these findings support the need for controlled randomized trials for other treatment options, including belimumab and epratuzumab for Sjögren's.

Citation

Letaief H, Lukas C, Barnetche T, Gaujoux-Viala C, Combe B, Morel J. Efficacy and safety of biological DMARDs modulating B cells in primary Sjögren's syndrome: systematic review and meta-analysis. *Joint Bone Spine*. 2018 Jan. 85(1);15-22.

RA Treatments Carry Higher Association with Non-Melanoma Skin Cancer in RA Patients

Researchers investigating the influence of corticosteroids and DMARDs on the association between rheumatoid arthritis (RA) and non-melanoma skin cancer (NMSC) found a significant association between certain drugs, dosage amounts and the number of drugs an RA patient takes with the risk for NMSC. Using data from the Taiwan National Health Insurance Research Database, 19,603 cases of newly diagnosed NMSC were identified between 1995 and 2013 and matched at a ratio of 1:1 to controls without NMSC. Comparably, RA patients had a significantly higher association with NMSC [(AOR)=2.23, 95% confidence interval (CI) 1.6-3.1, p<0.001]. This association was particularly strong in RA patients 65 years of age and older who used cyclosporine (AOR=5.7, 95% 2.2-14.86; ≥65 years: AOR=7.28, 95% CI 2.16-24.56), etanercept (AOR=5.27, 95% CI 1.15-24.27; ≥65 years: AOR=8.95, 95% CI 1.12-71.85), and d-penicillamine (AOR=4.79, 95% CI 1.63-14.12; ≥65 years: AOR=3.81, 95% CI 1.26-11.52). Additionally, RA patients using a cumulatively higher dose of corticosteroids and methotrexate (corticosteroids: >10g: AOR=2.96, 95% CI 1.67-5.22; >10g and ≥65years: AOR=3.5, 95% CI 1.77-6.92; methotrexate: 1-3g: AOR=2.57, 95% CI 1.13-5.82; >3g: AOR=4.64, 95% CI 1.74-12.4; >3g and ≥65 years: AOR=10.17, 95% CI 2.34-44.26) or using multiple kinds of DMARDS were at higher risk compared to non RA patients (any 3: AOR=3.72, 95% CI 1.67-8.26; any 5: AOR=2.81, 95% CI 1.13-7.04; any 6: AOR=5.23, 95% CI 1.14-24.14; 7-8: AOR=4.06, 95% CI 1.14-14.49).

Citation

Tseng H, Lu L, Lam H, Tsai KW, Huang WC, Shiue YL. The influence of DMARDs and corticosteroids on the association between rheumatoid arthritis and skin cancer: a nationwide retrospective case-control study in Taiwan. *Clin Exp Rheumatol*. 2017 Dec 15. [Epub ahead of print]

Decreased Risk of Dementia Associated with DMARD use in RA Patients

Using adults 18 years and older diagnosed with rheumatoid arthritis identified through the UK Clinical Practice Datalink, researchers sought to investigate the

impact that DMARDs had on dementia. In total, 3,876 DMARD users and 1,938 nonusers were identified in the database during the timeframe between 1995 and 2011. Using survival models, a lower risk of dementia was found in DMARD users compared to nonusers (HR: 0.60; 95% CI: 0.42–0.85). Of note, this difference was most notable in patients being treated with methotrexate (HR: 0.52; 95% CI; 0.34–0.82).

Citation

Judge A, Garriga C, Arden NK, Lovestone S, Prieto-Alhambra D, Cooper C, Edwards CJ. Protective effect of antirheumatic drugs on dementia in rheumatoid arthritis patients. *Alzheimers Dement* (N Y). 2017 Nov. 3(4):612-621.

Rheumatic Disease Patient Input on Glucocorticoid Use Reveals Benefits Outweigh Risks

The purpose of this study was to obtain patient input to identify beneficial and adverse effects (AE) of glucocorticoids (GCs) in patients with rheumatic diseases to help inform the development of a new patient-reported outcome measure. A cross-sectional survey was administered to two groups of patients, the first being rheumatic disease patients of a tertiary rheumatology clinic who had used GCs within the past year (n=55) and the second being patients from the Hospital for Special Surgery rheumatoid arthritis database, which identified both GC users (n=95) and non-users (n=29). Responses showed that many AEs were more frequently reported in GC users compared to nonusers. In all, 100% of respondents in group one and 86% respondents in group two reported experiencing at least one AE, the most severe being identified as skin thinning/easy bruising, sleep disturbance, mood disturbance and change in facial shape. In group two the prevalence per person was twice as high in GC users compared to nonusers (5.3 vs. 2.6; AE ratio, 2.0; 95% CI, 1.6–2.6). The majority of patients in each group (55% and 64%) reported that the benefits of GC's outweighed the AEs.

Citation

Black RJ, Goodman SM, Ruediger C, Lester S, Mackie SL, Hill CL. A survey of glucocorticoid adverse effects and benefits in rheumatic diseases: the patient perspective. *Journal of Clinical Rheumatology*: 2017 Dec. 23(8):416-420. doi: 10.1097/RHU.0000000000000585.

Effects of Immune Checkpoint Inhibitors on Patients with Rheumatic Disease

Researchers at the Mayo Clinic in Rochester, MN, sought to determine the risk of flares and adverse effects in patients with preexisting rheumatic diseases who then received immune checkpoint inhibitor (ICI) therapy. Investigators identified 16 patients with a variety of rheumatic diseases for inclusion through a retrospective review of Mayo Clinic patients who received ICI between 2011 and 2016. At the time of ICI initiation, seven patients were receiving immunosuppressive therapy or glucocorticoids for their respective diseases. Six patients (37.5%) experienced an immune-related adverse effect – in all cases the patients were successfully treated after discontinuing the ICI treatment.

Citation

Richter MD, Pinkston O, Kottschade LA, Finnes HD, Markovic SN, Thanarajasingam U. Brief report: cancer immunotherapy in patients with preexisting rheumatic disease: The Mayo Clinic experience. *Arthritis Rheumatol*, 70: 356–360. doi:10.1002/art.40397

Economic Burden of Arthritis Patients Continues to Increase

Researchers examined temporal trends in direct and out-of-pocket healthcare expenditures among arthritis patients in the U.S. and found that though per patient costs remained stable, the increase in arthritis patients amounted to a large increase in the economic burden on U.S. healthcare. Using data between 2008 and 2014 identified from the Medical Expenditures Panel Survey, researchers identified a cross-sectional cohort of adults 18 and older. Two-part models were used to estimate expenditures, which controlled for a variety of factors, including predisposing, enabling, need, personal health practice, and environmental factors. During the designated time period, the annual weighted arthritis population in the U.S. grew from 56.1 million to 65.1 million. In 2008, the annual mean direct expenditures were $10,424 (SE = $345, aggregate = $584.8 billion) and out-of-pocket expenditures were $1,493 (SE = $50, aggregate = $83.8 billion). In 2014, the annual average mean direct expenditures were $910 (SE = $279, total = $645.1 billion) and out-of-pocket expenditures were $1,099 (SE = $36, aggregate = $71.5 billion). Of note, findings from the researchers fully adjusted model revealed a significant increase in out-of-pocket and total expenditures from 2008 to 2014, though the degree of incremental out-of-pocket expenditures decreased during the same time period.

Citation

Raval A, Vyas A. Trends in healthcare expenditures among individuals with arthritis in the United States from 2008 to 2014. *The Journal of Rheumatology* Jan 2018, jrheum.170368; DOI: 10.3899/jrheum.170368

ACR Voices Support for Biosimilars

The American College of Rheumatology (ACR) has released a new white paper, entitled "The Science Behind Biosimilars – Entering a New Era of Biologic Therapy." Here, the ACR provides an overview of the important scientific, clinical and prescribing issues related to biosimilars, as well as the economic implications they may have. The authors note that, because a biosimilar should be therapeutically equivalent to the reference product on which it is based, the only anticipated advantage for biosimilars is a reduction in cost,

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which, in turn, can help to improve access to biologic drugs for patients. The white paper is available on ACR's website at: www.rheumatology.org/Portals/0/Files/ACR-White-Paper-Science-Behind-Biosimilars.pdf

Citation

Bridge Jr SL, White DW, Worthing AB, Gravallese EM, O'Dell JR, Nola K, Kay J, Cohen S. The science behind biosimilars – entering a new era of biologic therapy. *Arthritis & Rheumatology*. DOI 10.1002/art.40388

New Tool to Assess Health-Related Quality of Life in Sjögren's Patients

The purpose of this study was to develop and test a questionnaire, the PSS-QoL, to assess health-related quality of life in Sjögren's patients. The questionnaire consists of 25 questions in two main categories: physical and psychosocial. The tool's reliability was examined by having patients (n=75) complete the questionnaire once and then again between one and two weeks later. To assess construct validity, PSS-QoL scores were correlated with the ESSPRI (EULAR Sjögren's Syndrome Patient Reported Index), ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index), and EQ-5D (Euro-QoL 5D). Strong and moderate correlations were found between the PSS-QoL and ESSPRI (corrcoeff = 0.755) and EQ-5D (corrcoeff = 0.531). Reproducibility of the PSS-QoL yielded an ICC of 0.958 (95% CI: 0.926-0.981). Researchers believe the PSS-QoL could serve as a new patient-reported outcome measure in future clinical studies.

Citation

Lackner A, Stradner MH, Hermann J, Unger J, Stamm T, Graninger WB, Dejaco C. Assessing health-related quality of life in primary Sjögren's syndrome – the PSS-QoL. *Semin Arthritis Rheum*. 2017 Nov. pii: S0049-0172(17)30486-9. doi: 10.1016.

Treatment with Tregalizumab Misses Primary Endpoint in Phase IIb Trial

Researchers sought to evaluate the safety, efficacy and biological activity of tregalizumab in patients with rheumatoid arthritis who had previously been treated with methotrexate but showed an inadequate response. A total of 321 patients were randomly assigned to one of four treatment groups. One group received a placebo while the other three received a tregalizumab dosage of either 25mg, 100mg, or 200mg, respectively, once per week. At week 12 of the study, those who responded to their assigned treatment were kept in their original group. Conversely, those who didn't respond were either moved to the next higher dosage of tregalizumab or re-randomized from the placebo group into one of the tregalizumab treatment groups. The primary endpoint for this trial, the American College of Rheumatology's 20 Percent Improvement Criteria by week 12, was not met. Investigators monitored safety and biological activity through week 48 and found the expected biological effect on CD4 modulation. Tregalizumab was generally well-tolerated, with mild to moderate adverse events occurring comparably between tregalizumab and placebo groups. No additional safety findings were discovered through this trial.

Citation

van Vollenhoven RF, Keystone EC, Strand V, Pacheco-Tena C, Vencovský J, Behrens F, *et al*. Efficacy and safety of tregalizumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase IIb randomized, placebo-controlled trial. *Annals of the Rheumatic Diseases* Published Online First: 17 January 2018. doi: 10.1136/annrheumdis-2017-212478

Association Identified Between SLE and Atrial Fibrillation

By analyzing de-identified electronic health records (EHRs) from Vanderbilt University Medical Center, researchers have identified an association between systemic lupus erythematosus (SLE) and atrial fibrillation (AF). Data for SLE patients (n=1,097) and matched controls (n=5,735) were compared as was data between male and female SLE patients. The comparison between sexes found that males were more likely to experience AF then females [OR = 4.50 (FDR $p = 3.23 \times 10^{-3}$)]. A comparison between all SLE patients and the matched controls revealed a significant association between SLE and AF (p=0.002). Additionally, this finding also supports the process of using phenome-wide association studies as an EHR discovery tool for SLE. ■

Citation

Barnado A, Carroll RJ, Casey C, Wheless L, Denny JC, Crofford LJ. Phenome-wide association studies uncover a novel association of increased atrial fibrillation in males with systemic lupus erythematosus. *Arthritis Care Res*. 2018 February. doi:10.1002/acr.23553

Do we have your e-mail address?

If you want to receive all the latest updates from the Sjögren's Syndrome Foundation, then you should make sure we have your most up-to-date e-mail address! The SSF is sharing more information via e-mail, from news about the SSF and Sjögren's, to information about the latest treatments and medicines, to local Support Group updates and more. So contact us at ssf@sjogrens.org to be certain we have your latest e-mail address in our database, and then keep an eye out in your Inbox for Sjögren's news.

Just like all information you give the Foundation, your e-mail address will remain private and will never be given or sold to an outside organization.

Clinical News: Ocular

Economic and Psychological Impact of Sjögren's-Related Dry Eye

The purpose of this study was to examine the relationship between Sjögren's dry eye and medical expenditures, clinical severity and psychological status. A total of 64 patients, 34 with Sjögren's dry eye and 30 without, completed three self-report questionnaires to gather data, including: Ocular Surface Disease Index; Zung Self Rating Anxiety Scales, and; a questionnaire designed by the researchers of this study to examine patients' treatment, medical expenditures and income. Sjögren's dry eye patients were found to have an average annual expenditure of $1,174, with approximately $404 of that being paid by the patients themselves. These amounts were 5.5 ($p<0.001$) and 4.5 ($p<0.001$) times higher, respectively, compared to non-Sjögren's dry eye patients. Medication expenditure for both Chinese and western medicines were higher in the Sjögren's dry eye group, at 35.6 times ($p<0.001$) and 0.78 times ($p<0.001$), respectively. Additionally, indirect treatment-associated costs were 70% higher in the Sjögren's dry eye group and scores on the Zung Self Rating Anxiety Scale were positively correlated with total medical ($\rho = 0.399$; $P = 0.019$) and Chinese medicine expenditure ($\rho = 0.400$; $P = 0.019$).

Citation

Yao W, Le Q. Social-economic analysis of patients with Sjögren's syndrome dry eye in East China: a cross sectional study. *BMC Ophthalmology*. 2018 Feb. 18:23.

The Impact of an Exercise Program on Dry Eye Symptoms

The purpose of this study was to investigate the benefits of a cognitive behavior therapy-based exercise program to reduce the dry eye symptoms of office workers. As part of a larger group, 11 office workers with dry eye symptoms volunteered to participate in a home-based exercise program three days per week for 10 weeks. Investigators used the Dry Eye-Related Quality of Life Score and the World Health Organization's Subjective Well-Being Inventory Questionnaire to gain insight into body composition, dry eye symptoms and psychological distress. Both questionnaires were administered to participants pre- and post-intervention, though not every participant completed the program and/or questionnaires. Notably, participants with subjective dry eye reported significant improvements through the Dry Eye-Related Quality of Life Score after the intervention, suggesting that a cognitive therapy-based exercise program can aid in the treatment of patients with dry eye disease.

Citation

Sano K, Kawashima M, Takechi S, Mimura M, Tsubota K. Exercise program improved subjective dry eye symptoms for office workers. *Clin Ophthalmol*. 2018 Feb 9;12:307-311. doi: 10.2147/OPTH.S149986. eCollection 2018.

Elongases Identified for Synthesis of VLFCA-Creating Meibum Lipids

Researchers have identified the fatty acid elongases that are responsible for the synthesis of very long-chain fatty acids (VLFCAs) that create the meibum lipids. The elongation of VLFCA (ELOVL)1 is primarily responsible for producing saturated VLFCAs while ELOVLs 1,3 and 4 contribute in the synthesis of monounsaturated VLFCA's. The investigators found, in mice, that a disruption of ELOVL1 shortened acyl moieties in both cholesteryl and wax esters. These changes were associated with increases in eye-blink frequency and water evaporation from the ocular surface at younger ages. A development of corneal opacity with vascular invasion and epidermalization of the cornea were noted in aged ELOVL1 mutant mice. These findings help show that VLC meibum lipids can be characterized as barrier-forming lipids.

Citation

Sassa T, Tadaki M, Kiyonari H, Kihara A. Very long-chain tear film lipids produced by fatty acid elongase ELOVL1 prevent dry eye disease in mice. *The FASEB Journal*. 2018 Jan. doi/10.1096/fj.201700947R

Novel Contact Lens Capable of Measuring Ionic Concentrations in Tears

To help determine individual ion concentrations in tears, a team of researchers have developed a new silicone hydrogel contact lens sensitive to H3O+, hydronium cation, /OH−, hydroxyl ion and chloride ions, two important electrolytes in tear fluid. Developers were

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able to create a strongly bound hydrophobic ion sensitive fluorophores, unable to be washed away with aqueous solutions, by attaching hydrophobic C18 chains to water-soluble fluorescent probes for H3O+, hydronium cation, /OH−, hydroxyl ion and chloride. Potentially, this approach could be further developed to include capabilities for measuring the six dominant ionic species in tears and could help improve the ability to diagnose the various types of dry eye disease. ■

Citation

Badugu R, Jeng BH, Reece EA, Lakowicz JR. Contact lens to measure individual ion concentrations in tears and applications to dry eye disease. *Analytical Chemistry*. 2018 Feb. 542:84-94

Clinical News: Oral

A Comparison of Pilocarpine and Artifical Saliva to Treat Xerostomia and Xerophthalmia

This double-blind, randomized study was designed to compare the efficacy of pilocarpine and artificial saliva treatments for xerostomia and xerophthalmia in Sjögren's patients. The 72 participants were assigned to two groups, one receiving 10 drops of 5mg pilocarpine and the other receiving 10 drops of artificial saliva. Evaluations of the whole saliva, tear flow to globally assess dryness, and adverse effects were conducted at baseline and periodically throughout the 12-week study period. Compared to patients receiving artificial saliva, patients receiving the pilocarpine treatment showed statistically significant improvement in salivary flow ($p< 0.0001$), lachrymal flow ($p< 0.0001$), and their global assessment of dryness ($p< 0.0001$).

Citation

Cifuentes M, Del Barrio-Diaz P, Vera-Kellet C. Pilocarpine and artificial saliva for the treatment of xerstomia and xerophthalmia of Sjögren's syndrome: a double blind study. *Br J Dermatol*. 10.1111/bjd.16442

OHIP-14 Score Negatively Correlated with Pain, Salivary Flows, More

By using the guidelines for cross-cultural adaptation of health-related quality of life measures, researchers adapted the Brazilian version of the Oral Health Impact Profile-14 (OHIP-14) for a Portuguese cohort of Sjögren's patients. The adapted OHIP-14 was administered to 86 patients in conjunction with an analysis of whole saliva secretion rates and hyposalivation-related variables. Results found a significant negative correlation between the total OHIP-14 score, physical pain, physical disability domain and both stimulated and differential salivary flows. Additionally, a significant, negative, correlation was found between unstimulated salivary flow and physical pain.

Citation

Amaral J, Sanches C, Marques D, Vaz Patto J, Barcelos F, Mata A. Validation of Oral Health Impact Profile-14 and its association with hypossialia in a Sjögren's syndrome Portuguese population. *Acta Reumatol Port*. 2018 Mar 5. [Epub ahead of print].

Benefits Seen from Sialendoscopy in Sjögren's Patients

By irrigating the major salivary glands, researchers saw an enhancement in salivary flow and reduction in dry mouth after sialendoscopy in Sjögren's patients. Forty-nine Sjögren's patients were divided into three groups: control (n=15); irrigation with saline (n=16) and; irrigation with saline followed by triamcinolone acetonide (TA) in saline (n=18). A variety of measures, including unstimulated whole saliva flow, chewing-stimulated whole saliva flow, citric acid-stimulated parotid flow, Clinical Oral Dryness Score (CODS), Xerostomia Inventory (XI), and ESSPRI scores were collected one week prior to treatment as well as one, eight, 16, and 24 weeks after sialendoscopy. Patients in the saline-only intervention group saw significant increases in unstimulated whole saliva and chewing-stimulated whole saliva flow at eight weeks (P=0.013) and 24 weeks (P=0.004) while patients who received saline and TA saw significant increases at 16 weeks (P=0.035) and 24 weeks (P=0.03) as well as in citric acid-stimulated parotid flow at 24 weeks (P=0.03). Additionally, compared to controls, both intervention groups saw improvements in CODS, XI and ESSPRI scores. ■

Citation

Karagozoglu KH, Vissink A, Forouzanfar T, Brand HS, Maarse F, Jager DHJ. Sialendoscopy enhances salivary gland function in Sjögren's syndrome: a 6-month follow-up, randomised and controlled, single blind study. *Ann Rheum Dis*. Published Online First: 23 February 2018. doi: 10.1136/annrheumdis-2017-212672

Clinical News: Neurology

Treatment Response Predictors Identified for Sjögren's-Associated Neuropathy

A research team from India recently studied the clinical, electrophysiological spectrum, and therapeutic responses among the different subtypes of Sjögren's-associated neuropathy in order to identify predictors of suboptimal treatment response. Investigators used a retrospective cohort study design to identify patients with Sjögren's-associated neuropathies between January 2012 and November 2015, which resulted in 54 patients being identified. The majority of neuropathies were subacute-chronic (n=51) with the main subtypes being sensory ataxic neuropathy (n=17) and radiculoneuropathy (n=11). Atypical presentations included acute neuropathies, pure motor neuropathies, and hypertrophic neuropathy. Sensory ataxic neuropathy was associated with a greater severity and autonomic dysfunction. In all, improvements were found in 61% of patients (n=33). The best treatment responses were associated with cranial neuropathy and radiculoneuropathy.

Citation

Sivadasan A, Muthusamy K, Patel B, Benjamin RN, Prabhakar AT, Matthew V, Aaron S, Alexander M. Clinical spectrum, therapeutic outcomes, and prognostic predictors in Sjögren's syndrome-associated neuropathy. *Ann Indian Acad Neurol*. 2017 July-September. 20(3): 278-283.

CNS and PNS Mechanisms in Sjögren's: Potential Tool for Analysis

Using regional homogeneity (ReHo) analysis to provide clarity to the neurobiological mechanism of CNS and PNS involvement in Sjögren's, investigators collected data from 28 patients, 14 who had received a clinical diagnosis of Sjögren's and 14 age- and gender-matched controls, all of whom underwent functional magnetic resonance imaging in order to collect data. To compare data between groups, a double sample t-test was used. Sjögren's patients were found to have significantly increased ReHo values in the right cerebrum, left limbic lobe, right middle temporal gyrus and the inferior parietal lobe. Conversely, a significant decrease in values were found in the right lingual gyrus, left cuneiform lobe, left superior occipital gyrus, bilateral middle occipital gyrus and the fronto-parietal junction area ($p<0.01$, clusters >= 50 voxels). ■

Citation

Xing W, Shi W, Leng. Resting-state fMRI in primary Sjögren's syndrome. *Acta Radiologica*. doi/10.117/0284185117749993

Clinical News: Pulmonology

Steroid Pulse Therapy Successful in Treating Sjögren's Patient with Pulmonary Edema

A 67-year-old Sjögren's patient with pulmonary arterial hypertension developed pulmonary edema in reaction to upfront triple combination therapy. Providers subsequently aborted the dose escalation of epoprostenol, a pulmonary hypertension treatment, and initiated a continuous infusion of furosemide and noninvasive positive pressure ventilation. This strategy however, did not improve or prevent the worsening of pulmonary edema. After ruling out other possible causes for the edema, the providers identified pulmonary vasodilator-induced trans-capillary fluid leakage as a culprit, which was then successfully managed by steroid pulse therapy. The authors conclude that their strategy to stabilize trans-capillary fluid leakage by steroid pulse therapy should be considered as a treatment option in similar cases.

Citation

Takeuchi K, Nakayama K, Okano M, Tamada N, Suehiro H, Shinkura Y, Yanaka K, Onishi H, Tanaka H, Shinke T, Emoto N, Hirata K. Upfront triple combination therapy-induced pulmonary edema in a case of pulmonary arterial hypertension associated with Sjögren's syndrome. *Respiratory Medicine Case Reports*. 2018 Jan. 23;55-59.

Unexplained Cough and Sjögren's

The purpose of this study was to evaluate patients with an unexplained cough for undiagnosed Sjögren's. A total of 24 patients were identified from a single location, 22 of which agreed to participate in the evaluation. Included patients presented with an unexplained cough and concomitant dry eye and were evaluated by pulmonologists, rheumatologists and ophthalmologists specializing in autoimmune disease. Patients were asked to complete a variety of tests, including the Leicester Cough Questionnaire, spirometry, antibody testing and a series of ophthalmologic exams. At four years, a follow-up questionnaire was administered via telephone. Of the 22 patients involved, eight were diagnosed with Sjögren's. At follow-up, 37% of the Sjögren's patients reported that their cough improved while 64% of patients without Sjögren's noted improvement. This finding supports the consideration for adding an unexplained cough to the diagnostic algorithm for Sjögren's. ■

Citation

Koslow M, Kivity S, Vishnevskia-Dai V, Ben-Dov I. Unexplained cough: it is time to rule out Sjögren's syndrome. *Clinical Rheumatol*. 2018. doi/10.1007/s10067-018-3987-4

The National Dental Practice-Based Research Network
The nation's network

Research UPDATES

Dental Care for Patients Taking Bone Protecting Drugs

Many people with osteoporosis (weak bones) take medications, called bisphosphonates, which help reduce their risk of having a bone fracture. People with osteoporosis commonly take bisphosphonates in a pill, while cancer patients often receive a high-dose injection.

Your dentist is part of the National Dental Practice-Based Research Network, a group of dental practices that treat patients and also do dental research. For more information go to **www.nationaldentalpbrn.org.**

Risks for a rare condition: osteonecrosis of the jaw (ONJ)

ONJ is a rare disease in which an area of the jaw bone starts to die because it's not getting enough blood. Researchers and dentists in the National Dental Practice-Based Research Network conducted two studies to determine the chance that someone will have ONJ, and what factors may increase these chances, such as oral bisphosphonates.

Findings from the studies show that ONJ is very rare, but bisphosphonates increase the risk of developing it.

- In a study of 572,000 dental patients, only 23 patients had ONJ (about 4 per 100,000 patients).
- The risk of ONJ was 9 to 12 times greater for study participants who took bisphosphonates than for those who didn't.
- Only 6 of the 23 ONJ patients had taken oral bisphosphonates.
- A study of 191 ONJ patients showed that the stronger the bisphosphonate dose the greater the ONJ risk.
- Having a tooth pulled also increased the risk of developing ONJ.

What to do

Talk with your dentist if you currently take or are planning to take bisphosphonates for your bone health. If possible, address any existing dental care needs before beginning bisphosphonate treatment.

Do not avoid dental care if you currently take bisphosphonates, since your risk of ONJ following dental surgery is very low.

Protect your bones:

- Eat foods rich in calcium and vitamin D.
- Do plenty of strength-building and weight-bearing exercises, such as walking, climbing stairs, lifting weights, and dancing.
- Do not use tobacco.
- If you drink alcohol, drink in moderation.

More information on protecting your bones is at the National Institute of Arthritis and Musculoskeletal and Skin Diseases www.niams.nih.gov/Health_Info/Bone/.

References: Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Annals of Internal Medicine* 2006;144(10):753-761.
Fellows JL, Rindal DB, Barasch A, Gullion CM, Rush W, Pihlstrom DJ, Richman J. ONJ in two Dental Practice-Based Research Network Regions. *Journal of Dental Research.* 2011;90(4):433-438.
Barasch A, Cunha-Cruz J, Curro FA, Hujoel P, Sung AH, Vena D, Voinea-Griffin AE; CONDOR Collaborative Group, et al. Risk factors for osteonecrosis of the jaws: a case-control study from the CONDOR Dental PBRN. *Journal of Dental Research.* 2011;90(4):439-444.

Funded by National Institutes of Health grant U19DE22516

To ensure excellent dental care, the Network carries out our studies in real-world settings—like your dentist's office—with regular patients like yourself who volunteer to participate. The studies wouldn't be possible without the involvement of our wonderful patients.

Thanks to everyone who participated in this and all of our studies!

Industry News

Shire Institutes Open-Access Research Policy

Effective January 2, 2018, Shire has instituted an open-access program for research, which includes journals the company has funded. This move essentially removes the barrier to subscription journals, allowing the public free access to the company's research without having to wait long after publication, allowing others to build on and learn from Shire's research.

Phase IIb Study for Reproxalap Begins

Patient enrollment has begun for the Phase IIb study of Reproxalap, an aldehyde-binding molecule that works to mitigate excessive inflammation caused by excessive aldehydes. According to Aldeyra Therapeutic's, the primary endpoints for this study are safety and efficacy, with initial data expected to be available in late 2018.

Novaliq's NOV03 Moves to Phase II Trial

Novaliq has begun enrolling patients in a Phase II trial for NOV03, a drug designed to enter deep into the meibomian gland to dissolve meibomian lipids and help improve gland functionality. This multi-center, randomized, double-masked, saline controlled study will evaluate the efficacy of using NOV03 twice and four times daily, with top-line data expected to be available in late 2018.

Interactive Resources Available from the NIH Pain Consortium

The NIH Pain Consortium's Centers of Excellence in Pain Education consists of 11 universities that serve as hubs for the development, evaluation and distribution of online training modules to enhance and improve how health care professionals can learn about pain and the subsequent treatments. Recently, a variety of interactive modules were made available, including one featuring a patient with chronic burning pain in her mouth. This, and other modules, can be found at www.painconsortium.nih.gov.

Hanmi & Lilly Discontinue Phase II Trials of BTK Inhibitor

Global Phase II trials of the use of Hanmi Pharma's Bruton's Tyrosine Kinase (BTK) inhibitor in rheumatoid arthritis patients have been discontinued after producing results which indicate the drug could fail to demonstrate its target effectiveness. Hanmi originally signed a licensing-out deal with Eli Lilly in 2015, and is now considering continuing to develop the drug for new indications.

RegeneRx Receives US Patent for Tβ4

RegeneRx, a clinical-stage, biopharmaceutical company, has received a U.S. patent for Thymosin Beta 4 (Tβ4) for use in dry eye syndrome. Tβ4 is the active ingredient in RGN-259, a preservative free, eye drop designed for patients suffering from moderate to severe dry eye. A meeting with FDA between RegeneRx's U.S. joint venture, ReGenTree LLC, is schedule for April of this year.

MedImmune Launches New Company – Viela Bio

Medimmune Inc, a branch of AstraZeneca, has launched a new company, Viela Bio, which will focus on six experimental drugs for a variety of indications, including Sjögren's and myositis, both of which are in early stage human trials. The new company has received nearly $250 million in funding from a variety of investors and will be led by Bing Yao, formerly a Senior Vice President with MedImmune.

New Publications Demonstrate Effectiveness of Lipiflow®

Johnson and Johnson Vision announced the publication of two studies whose results provide evidence of the benefit of Lipiflow® treatment for meibomian gland dysfunction (MGD). Results from the first study saw an improvement in average MGD function and a reduction in dry eye signs and symptoms for soft contact lens wearers over a period of three months. Results from the

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second study found that a single Lipiflow® treatment was significantly more effective in treating dry eye symptoms associated with MGD compared to a three month course of doxycycline treatment taken daily. No adverse events were reported in either study, both of which were funded by TearScience, a division of Johnson & Johnson Vision.

Blackie CA, Coleman CA, Nichols KK, Jones L, Chen PQ, Melton R, Kading DL, O'Dell LE, Srinivasan S. A single vectored thermal pulsation treatment for meibomian gland dysfunction increases mean comfortable contact lens wearing time by approximately 4 hours per day. *Clin Opthalmol*. 2018 Jan 17;12:169-183. doi: 10.2147/OPTH.S153297. eCollection 2018.

Hagen KB, Bedi R, Blackie CA, Christenson-Akagi KJ. Comparison of a single dose vectored thermal pulsation procedure with a 3-month course of daily oral doxycycline for moderate-to-severe meibomian gland dysfunction. *Clin Opthalmol*. 2018; 12: 161–168. Published online 2018 Jan 17. doi: 10.2147/OPTH.S150433

New Collaboration Between Aldeyra Therapeutics and Janssen Research & Development

Aldeyra Therapeutics and Janssen Research & Development, a Johnson & Johnson company, have agreed to a new collaboration, which will focus on developing drugs to address a new class of therapeutic targets, pro-inflammatory aldehyde mediators. Currently, the leading program is reproxalap, details of which are mentioned previously in this issue of *Sjögren's Quarterly*. No financial details have been released at this time.

ImmunoQure AG Partners with Servier on SLE and Sjögren's Therapy

A new collaboration between German-based ImmunoQure AG and French-based Servier will focus on advancing previous work looking into interferon alpha autoantibodies. Elevated levels of interferon alpha, a protein that plays a role in the ability of the human immune system to defend against viruses, have been consistently found in patients with systemic lupus erythematosus. Researchers believe that we may be better able to treat autoimmune diseases, such as SLE and Sjögren's, by blocking this protein. The two companies are working to prepare the autoantibody for interferon alpha for preclinical tests, and eventually, clinical trials. In addition to payments from Servier that are expected to total approximately $200 million, ImmunoQure will also receive royalties on net sales.

Alcon to Increase Awareness Efforts on Digital Eyestrain

At a recent press conference, an Alcon spokesperson shared results from a patient survey looking into eyestrain caused by digital devices. The company partnered with Esen K. Akpek, MD, and the Institute for the Future, to help conduct the survey, which acquired feedback from 6,000 people aged 18 years or older from six countries. Of note, 66% of U.S. respondents reported they experienced dry eye symptoms after extended use of digital devices on a weekly basis. With this information, Alcon hopes to create additional awareness of the risks in digital eyestrain.

Patent Granted for Novel Artificial Salivary Gland

Oral Fluid Dynamics LLC, a Connecticut-based startup, has received a patent for a novel artificial salivary gland design. Though still under development, the idea is that the artificial gland would collect and alter existing fluid, such as fluid from around cells and bone marrow fluid, so that it would then resemble naturally occurring saliva. After being implanted in a patient's jaw, the device would be activated through contact with the teeth and chewing motions.

Wize Pharma Enrolls First Patient in Phase IV Study of LO2A

Wize Pharma, an Israel-based clinical-stage biopharmaceutical company, has enrolled their first patient in a Phase IV clinical trial to investigate LO2A as a symptomatic treatment for dry eye syndrome in Sjögren's patients. This randomized, double-masked study will include approximately 60 Sjögren's patients and compare LO2A to Systane® Ultra UD, an over-the-counter treatment from Alcon. The primary endpoint of this study is the change in corneal/conjunctival staining after three months using the National Eye Institute Industry Grading System. The study design will also support clinical approval pathways for LO2A as a treatment for dry eye syndrome in patients with Sjögren's in the U.S. and China.

Ocugen's OCU310 Clears Phase II Trial

A Phase II trial of OCU310, a combination of brimonidine tartrate and loteprednol etabonate, both of which are already approved, demonstrated an improvement in a variety of dry eye disease symptoms after 12 weeks of treatment compared to a placebo. A company spokesperson has stated that Ocugen is looking forward to presenting the full research results from the trial and having further discussions with the FDA regarding OCU310.

Vobarilizumab Misses Primary Endpoint in Phase II Trial.

Vobarilizumab, a product of Belgium-based biopharmaceutical company Ablynx, has failed to meet its primary endpoint and did not detect a dose response at 24 weeks in systemic lupus erythematosus patients based on the modified BILAG-based combined lupus assessment (mBICLA). In January, it was announced that Sanofi will acquire Ablynx as part of a $4.8 billion takeover, which includes the acquisition of vobarilizumab. ■

SSF In Action

SSF Submits Ideas for NIH *All of Us* Research Program and Participates in Workshop

NIH's *All of Us* Research Program is being coordinated with the purpose of building one of the largest, most diverse datasets ever in order to help expedite research on a wide array of health conditions. Between January and February, 2018, the program solicited public input, asking for research ideas that the program could uniquely address while allowing public comments and votes. During this period the SSF submitted 13 research ideas related to various aspects of Sjögren's and autoimmune diseases for consideration. In total, these ideas received more than 300 votes of support from the public.

In March, Matt Makara attended a three-day workshop in Bethesday, MD, to review, discuss and prioritize research ideas. An overview of the outcomes from this workshop will be included in the Summer issue of *Sjögren's Quarterly*.

SSF Attends Inaugural Ocular Surface Disease Symposium

From left to right: Leslie E. O'Dell, OD, FAAO; Louise Sclafani, OD, FAAO; S. Barry Eiden, OD, FAAO; Jennifer S. Harthan, OD, FAAO, FSLS; Casey L. Hogan, OD, FAAO, FSLS; Matt Makara, MPH; Laura Periman, MD; John Conto, OD, FAAO; Stephanie Messner, OD, FAAO; Scott Schachter, OD; Eric Baas, OD, FAAO

On January 28, 2018, the Illinois College of Optometry held their inaugural Ocular Surface Disease Symposium in Chicago, IL. This event, which saw nearly 400 attendees, was due in large part to the efforts of Casey Hogan, OD, FAAO, who is a Sjögren's patient and SSF member herself. This event provided attendees the opportunity to hear from numerous ocular disease experts from around the country on a variety of topics, including updates on the classification, definition and pathophysiology of ocular surface disease, understanding diagnostics related to ocular surface disease, and therapeutics and treatment options for ocular surface disease.

As part of her morning presentation, Dr. Hogan spoke about her personal journey with Sjögren's and why organizing an event like this was so important to her. At the conclusion of her presentation, the SSF's Matt Makara was invited to the stage to say a few words about the Foundation and receive, on behalf of the SSF, a very generous donation of $5,000 from the Illinois College of Optometry. The SSF was also provided a table to display materials and, throughout the day, those who visited the SSF exhibit table had the opportunity to learn more about Sjögren's and walk away with valuable resources.

The SSF thanks Dr. Hogan, the Illinois College of Optometry, and all who attended and helped organize this event for their generosity and continued interest in Sjögren's and support of the Foundation.

SSF Attends NHC Training on Quality Measures

The SSF's Matt Makara attended a full day training on February 15, 2018, hosted by the National Health Council entitled, "Ensuring the Patient Voice in Quality: An Educational Program for Patient Groups and Advocates." This educational session included six modules on various topics related to quality, including why quality matters for patients, where quality measures come from and the role of quality in value-based payment. Additionally, the training included ample time for groups to discuss how these concepts could be applied to the work of the patient advocacy groups present that day. Key concepts from this training will be made publicly available later this year.

SSF's Taylor Participates in NHC's 2018 Health Leadership Conference

This year's National Health Council (NHC) 2018 Health Leadership Conference was held in Fort Lauderdale, FL, between February 7-9, 2018. Among other presentations, the NHC's Marc Boutin, JD, provided

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a "State of the Council" in which he spoke about the need to "confront our environments" and "clarify our mission's focus" to help take our work in the social sector from good to great. Additionally, the SSF's Steven Taylor participated in a panel discussion on measuring impact in which he shared the SSF's successes of the 5-Year Breakthrough Goal. Taylor is currently serving as Chairperson-elect on the NHC Board of Directors.

SSF Attends NIDCR Symposium on Autotherapies

On January 25, the SSF's Matt Makara attended the NIDCR-sponsored symposium, "Autotherapies: Enhancing Our Innate Healing Capacity," at the NIH Clinical Center in Bethesda, MD. The event featured a variety of speakers with expertise in stem cell biology, craniofacial anomalies and regeneration, regenerative bioengineering and cancer immunotherapy both from within NIH as well as external U.S. research institutions. A recording of this half-day symposium is available at https://videocast.nih.gov/summary.asp?live=26885&bhcp=1.

SSF Visits NIH as Part of FNIDCR

Representatives from the FNIDCR Patient Advisory Council with NIDCR staff at NIH

As part of the Friends of the National Institute of Dental and Craniofacial Research (FNIDCR) Patient Advisory Council (PAC), the SSF's Kathy Hammitt, who is currently serving as council chair, and Matt Makara visited the NIH campus in Bethesda, MD, to meet with NIDCR leadership. This visit allowed PAC members to learn more about the NIDCR from a variety of NIDCR staff, including a high-level overview of the Institute from Dr. Martha Somerman, Director, NIDCR, and both the Extramural Research Program and Intramural Clinical Research Center Programs from Drs. Lillian Shum and Janice Lee, respectively. Additionally, the group discussed ways in which the institute and council could better engage and support the work of one another.

SSF Attends Briefing on PDUFA VI Implementation

On January 18, the SSF's Matt Makara attended a briefing entitled, "PDUFA VI Implementation: What's Next?," hosted by PhRMA in Washington, D.C. This new iteration of the law provides FDA with the resources needed to maintain a predictable and efficient review process for human drug and biologic products. The briefing offered attendees a glimpse into what can be expected during the next few years as a result of PDUFA VI as well as suggestions and opportunities for how stakeholders can engage with the FDA.

SSF Attends FDA CDER Workshop on Engaging with FDA

On Tuesday, April 3, 2018, Matt Makara, the SSF Director of Research and Scientific Affairs, attended an FDA-hosted workshop entitled, "CDER and You: Keys to Effective Engagement." Throughout the day, a variety of presenters, including FDA staff as well as representatives from patient advocacy groups, provided information on best practices for working with the FDA as well as the various pathways that are available to pursue, including patient-focused drug development meetings, the Patient Representative Program and listening sessions. In addition to providing overviews of the FDA Center for Drug Evaluation and Research, FDA representatives demonstrated their new, more efficient, system for non-industry stakeholders to request meetings and spoke about the draft guidance on methods for collecting patient experience data from external stakeholders. This guidance, due to be available in June 2018, will be the first in a series of related guidance documents. Additionally, to help review important and useful information, attendees formed teams to play FDA Jeopardy, which proved to be a great way to drive home key points. ■

John Whyte, MD, MPH (at the podium) and Matt Makara, MPH (seated far right)

Sjögren's Syndrome Foundation

Patient Education Sheet

Pregnancy in Sjögren's

Nancy Carteron, MD, FACR
Senior Consultant, Rheumatology Immunology
Clinical Faculty, University of California San Francisco

Most women will conceive and have healthy babies. However, there are potential complications. Consulting your obstetrician (OB-GYN), rheumatologist, and possibly a high-risk OB (perinatologist) prior to conceiving or early in pregnancy is suggested.

Factors contributing to the ability to conceive:

- Age
- Primary ovarian failure
- Endometriosis
- Environmental factors (i.e. pesticides)

Potential pregnancy complications:

- Congenital heart block (SSA/SSB autoantibodies; possibly RNP antibodies)
- Neonatal lupus (rash) (SSA/SSB autoantibodies)
- Fetal loss
- Intrauterine growth retardation
- Premature delivery
- Recurrent pregnancy loss
- Preeclampsia (phospholipid autoantibodies)

Know your autoantibody (blood tests) status:

- SSA (Ro) and SSB (La) – higher levels may carry more risk
- Phospholipid antibody (APL) – Lupus anticoagulant; IgG and IgM cardiolipin antibody; IgG and IgM anti-beta2 glycoprotein I antibody

Congenital heart block (CHB) – most serious potential complication:

- First pregnancy – 2 % risk
- If previous child had CHB, risk increases 10-fold for subsequent pregnancy
- Weekly Doppler fetal echocardiogram surveillance between the 18th and 20th weeks
- Cardiomyopathy can occur
- Management strategies, including fetal pacemaker available

Neonatal lupus (rash):

- Autoantibodies cross the placenta, decline over several weeks, rash resolves
- If previous child had neonatal lupus, risk increases 5-fold for neonatal rash for subsequent pregnancy

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

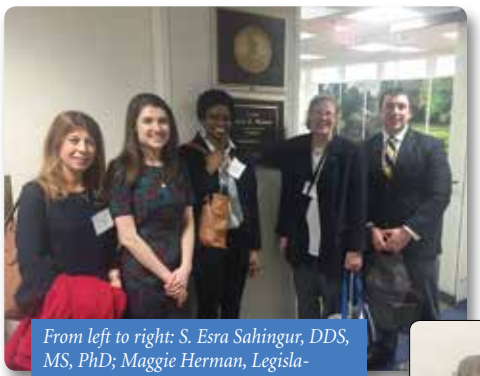
SSF Participates in AADR FNIDCR Advocacy Day on Capitol Hill

On Tuesday, February 27, the SSF's Kathy Hammitt and Matt Makara participated in the American Association for Dental Research (AADR) & Friends of the National Institute of Dental and Craniofacial Research (FNIDCR) Advocacy Day on Capitol Hill. The SSF joined other advocates, researchers, students and AADR staff for an informative morning session in which attendees learned about the NIDCR's history and research efforts from Martha Somerman, DDS, PhD, Director, NIDCR, as well as a legislative and political update and overview from Representative Mike Simpson, DMD (R-ID). The morning session concluded with Hammitt providing remarks on the need for continued advocacy for increased funding for dental and craniofacial research.

The afternoon afforded SSF staff and others the opportunity to meet with congressional offices from their home states. In all, the SSF participated in four meetings with congressional staffers from Virginia offices to discuss patient stories, research and the critical need for sustained and increased funding for NIH and NIDCR. The SSF thanks all staffers who provided their time and input when meeting with participants of this day's event.

Acknowledging the importance of advocacy, the SSF helped sponsor the AADR FNIDCR Day on Capitol Hill, which helped to fund the attendance of students and advocates living outside the greater D.C. Metro Area. ■

Kathy Hammitt, MA (Left) and S. Esra Sahingur, DDS, MS, PhD (right), with a staffer from Congressman Bob Goodlatte's office



From left to right: S. Esra Sahingur, DDS, MS, PhD; Maggie Herman, Legislative Correspondent for Senator Mark Warner; Seun Ajiboye, PhD; Kathy Hammitt, MA; Matt Makara, MPH

From left to right: Kathy Hammitt, MA; Seun Ajboye, PhD; Congressman Don Beyer (D-VA); S. Esra Shingur, DDS, MS, PhD; Matt Makara, MPH