Proceedings of the Sjögren's syndrome Foundation National Conference

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The Sjögren's Syndrome (SS) Foundation National Patient Conference held in Reston, VA, USA, April 20–21, 2007, featured a variety of lectures and workshops on various aspects of the disease presented by speakers of national prominence. The conference included over 430 participants from 38 states and three foreign countries including India, the UK and Canada. On April 21, conferees discussed a wide spectrum of topics, including extraocular and extraoral manifestations, associated autoimmune diseases, laboratory abnormalities and novel approaches to treatment.

Overview of autoimmune disease

Antony Rosen, Johns Hopkins University, NY, USA, presented an overview of autoimmune disease. Autoimmune diseases are extrodinarily complex but provide an unparalled opportunity to investigate regulation of the immune system. Complexity arises from the diversity of the affected population, heterogeneity in disease phenotype and overlapping clinical manifestations. In SS, antibodies primarily target Ro/La, α and β fodrin, NuMA, M3-R, golgins and poly (ADP-ribose) polymerase, although many potential additional protein and gene polymorphisms may contribute to disease susceptibility and phenotype. High-throughput DNA sequencing and chip-based antibody and gene expression microarray analysis have a high likelihood of identifying potential immunopathogenic molecules in SS. Enhanced expression of interferon (IFN) regulatory genes has been found in the mononuclear cells of patients with systemic lupus erythmatosus (SLE) and normal mononuclear cells treated with IFN-γ. Recently, similar upregulation of IFN regulatory genes has been observed in salivary gland tissue obtained from SS patients, thus identifying a potential site for immunological therapeutic intervention. Studies of genes involved in salivary gland cell death and repair also have a high potential to yield information regarding important pathologic pathways in SS.

Overview of SS manifestations

Steven E Carsons, Winthrop-University Hospital, SUNY Stony Brook, NY, USA, presented an overview of the manifestations of SS. SS is a prototype systemic autoimmune disorder comprised of an organ-specific and a multisystem component. In addition to the well recognized xerostomia and xeropthalmia, sicca symptoms may occur in the nasal mucosa, the tracheo–bronchial tree and the genital tract owing to the wide anatomical distribution of exocrine glands. In addition, lymphocytic infiltration may result in pulmonary parenchymal disease as well as autoimmune hepatitis and renal tubular disease. Elevated circulating levels of immunoglobulin, often containing antibody to SS-A and SS-B, may result in a leukocytoclastic vasculitis manifesting as palpable purpura. Approximately 50% of patients experience neurological disease, with peripheral neuropathy occurring most commonly. Cranial neuropathy, particularly trigeminal neuralgia, is strongly associated with SS. CNS disease is felt to be rare. Many studies demonstrate that SS patients have an approximate 15–40-fold enhanced risk for the development of lymphoma when compared with an age-matched population. Lymphoma in the setting of SS is often an extranodal, marginal zone, B-cell tumor involving mucosa associated lymphoid tissue (MALT). Emergence of a monoclonal protein, cryoglobulinemia, palpable purpura and C4 hypocomplementemia may herald lymphoma development. Fatigue has been identified as a significant problem in certain patients and is most likely multifactorial. Chronic inflammation, endocrinopathy (hypothyroidism), sleep disorder and secondary fibromyalgia may contribute to fatigue. Demonstration of ocular dryness and corneal dysfunction, diminished salivary flow, abnormal salivary gland imaging, the presence of antibody to SS-A and SS-B and focal lymphocytic sialadenitis on minor salivary gland biopsy are important diagnostic findings. Classification criteria have been developed to aid in the characterization of patient populations.

Disability issues

Thomas D Sutton, Leventhal, Sutton and Gornstein, PA, USA, discussed disability issues. In order to qualify for disability benefits under the US Social Security Administration, an individual must meet five qualification steps:

- Demonstrate gainful work activity
- Have medical evidence of a significant impairment that has an impact upon the performance of work-related activities

- Have an impairment that is of the severity that meets the listing of impairments in the regulations
- Does not possess the residual functional capacity to return to past relevant work
- Cannot perform any other work in the national economy

SS patients may experience particular difficulty in the above process with regard to points two and three. Primary Sjögren's patients, who by definition do not demonstrate evidence of rheumatoid arthritis (RA) or SLE, may be denied benefits because the adjudicators do not appreciate the degree of symptomatology associated with Sjögren's – for instance adjudicators may regard sicca symptoms as minor and not realize that they may lead to the inability to communicate, affect the ability to obtain proper nutrition, cause visual impairment and so on. Moreover, there is no regulatory listing specific for SS. Therefore, claimants must individually demonstrate that their impairment is equivalent to a listing given for another autoimmune connective tissue disorder. Interestingly, keratoconjunctivitis sicca (KCS) is present in the listing as an extra-articular manifestation of RA. Nonetheless, several US Federal Court rulings have recognized the impact of SS on the ability of individual patients to sustain gainful employment. As a result of advocacy by the SS Foundation, the US Social Security Administration has proposed to add a new section to the listing, which would address Sjögren's. Specifically, the listing would be met if a claimant demonstrates at least two organs/body systems involved along with two constitutional symptoms. Alternatively, the patient may have lesser organ system involvement but two constitutional symptoms and marked limitation in one of the following: activities of daily living, maintaining social functioning or timely task completion.

New concepts in the management of dry eye

Gary N Foulks, University of Louisville, KY, USA, discussed dry eye management. Dry eye is a multifactorial disorder involving the tears and ocular surface, resulting in symptoms of discomfort, visual disturbance and tear-film instability. Dry eye is subclassified into aqueous-deficient and evaporative forms. Dry eye associated with SS belongs to the aqueous-deficiency subgroup. Other dry eye syndromes caused by aqueous deficiency include lacrimal gland dysfunction or obstruction and effects of systemic drugs. Dry eye syndromes secondary to evaporative causes include Meibomian deficiency, lid dysfunction, vitamin A deficiency, contact lens use and allergy. Pathophysiologically, these conditions lead to increased tear osmolality, which can cause cellular dehydration, activation and subsequent ocular surface inflammation.

Optimal treatment of dry eye, in part, depends on the etiology. Evaporative dry eye is best approached using lid care and tearfilm stabilization; the latter can be accomplished employing lipid containing topical emulsions. Aqueous deficiency is treated by osmoprotection, with preparations of artificial tears that reduce tear osmolality as well as by surface protection utilizing eyedrops that contain polymers such as polyethylene glycol 400 and propylene glycol. Both forms of dry eye may benefit from anti-inflammatory therapy and the use of microenvirnonmental glasses. The current mainstay of topical anti-inflammatory treatment is cyclosporine ophthalmic (Restasis®), which has been shown to increase Schirmer scores and increase goblet cell density in controlled clinical trials. Oral supplementation with essential fatty acids may have an ocular anti-inflammatory effect. Therapy with linoleic acid and γ-linoleic acid has been shown to improve dry eye symptoms, Lissamine green staining and ocular surface inflammation. Topical and systemic therapies may be utilized in an attempt to stimulate tear production. Topical preparations containing diquafosol have been demonstrated to decrease corneal staining. Oral pilocarpine and cevemiline have been shown to improve dry eye symptoms. Punctal occlusion may be accomplished transiently using cyanoacrylate or collagen adhesives; temporarily using silicone plugs or permanently by laser, electrocautery or suture.

SS & contact lenses

Peter C Donshik, University of Connecticut Health Center, CT, USA, presented a talk on SS and contact lenses. The ability to tolerate and the clinical utility of contact lenses for the Sjögren's population is quite variable. Contact lenses have the propensity to exacerbate dry eye symptomatology by disrupting the tear film and mucus production, affecting lipid spreading and by increasing tear evaporation, leading to tear hypertonicity. Contraindications to lens wear include moderate-to-severe KCS with ocular surface disease, chronic lid disease and abnormalities in lid function or blinking. On the other hand, certain lenses may be therapeutic for the patient with severe dry eye refractory to other treatment modalities. Strategies to help the dry eye patient tolerate contact lenses include appropriate choice of the lens care system, the physicochemical properties of the lens itself and optimal utilization of modalities to increase tear production and volume. Lenses composed of omaflicon A, a 60% equilibrium water content hydroxyethylmethacrylate hydrogel, resulted in reduced symptoms of dry eye and decreased flourescein staining compared with control lenses. Lenses made from silicon hydrogels also result in fewer subjective complaints of dryness. These lenses appear to cause less on-eye dehydration secondary to their low-water content. Silicone lenses possessing a high oxygen permeability factor reduce corneal hypoxia and aid in lens tolerability. Therapeutic soft contact lenses may aid the treatment of filamentary keratitis and corneal ulcers. The Boston scleral contact lens is an ocular prosthetic device that contains a fluid reservoir, thus creating a liquid corneal bandage. Although large and bulky, these devices can reduce corneal inflammation, pain and photophobia and promote resurfacing of epithelial defects. Some of the most severe cases of dry eye are seen in chronic graft-versus-host disease (cGVHD). Of 33 cGVHD patients (61 eyes) fitted with liquid corneal bandage lenses, the vast majority (73–91%) experienced moderate to significant improvement in pain, photophobia, quality of life, reading and driving. In terms of

overall contact lens status in SS patients, a study of 17 patients revealed that 82% were wearing lenses at 3 months.

Assessing symptoms of chronic dry eye & effects on quality of life

Kelly Nichols, Ohio State University, OH, USA, spoke on the symptoms of dry eye and the effects it has on overall quality of life. Symptoms have been an integral component of the evolving definition of dry eye, beginning with the National Eye Institute (NEI)/industry workshop on clinical trials in 1995 and the subsequent NEI workshop in 2001/2002. The dry eye workshop provided agreement regarding symptoms and included quality-of-life items. The prevalence of moderate to severe dry eye based on symptomatology is approximately 9 million US residents. Women are affected approximately at least twice as often as men. The prevalence of dry eye increases with advancing age. The NEI Visual Function Questionnaire (NEI-VFQ-25) has eight vision-related dimensions including ocular pain. The ocular pain subscale is comprised of two questions designed to determine the degree of ocular pain experienced from burning, itching or aching; and to what degree the pain prevents the patient from doing what they would like. Lower scores indicate higher symptomatology and poorer functionality. In comparison to a reference score of 90 ± 15 units, dry eye patients scored 70 ± 19 units. When assessing symptoms, it is important to identify the most appropriate questions. Symptom frequency and severity are highly correlated, whereas dryness, discomfort/irritation, itching/light sensitivity and grittiness are most often reported. Symptoms often correlate poorly with diagnostic tests. Symptoms have different levels of impact; the worst symptom is not always the most bothersome to the patient. Symptoms at the end of the day are generally worse. Patients with dry eye syndrome were more likely to report problems with reading, professional work, using a computer, watching television and driving (odds ratios ranging from 2.2 to 3.6). Patients with SS have lower Short Form-36 scores than the adjusted norm. Sjögren's patients with advanced corneal staining appear to have fewer dry eye symptoms than patients with less staining. Among patients fulfilling American–European criteria for SS, strong associations between the NEI-VFQ and the ocular surface disease index (OSDI) were observed for VFQ ocular pain and mental function subscale and the OSDI symptoms subscale and the VFQ general vision, ocular pain, mental function, role function and driving and the OSDI function subscale.

Salivary gland dysfunction & its managament

James J Scuibba talked on management of salivary gland dysfunction. There are multiple causes of salivary dysfunction, including medication, radiation therapy, SS, duct obstruction, anxiety, HIV and aging. Chronic salivary dysfunction results in alterations in mucous membranes, tooth decay, periodontal disease, fungal infection, swallowing dysfunction, difficulties with speech and alteration of taste. Autoimmune salivary dysfunction, as typified by SS, causes salivary dysfunction by destruction of exocrine glandular tissue and by mediating dysfunction of remaining secretory units. Dysfunction of remaining secretory units may be caused by aberrant neuroepithelial/myoepithelial interactions and by interference with muscarinic M3 receptor signaling, perhaps by autoantibodies. In SS, involvement extends to serous and mucous-producing salivary glands and minor mucous-producing glands at numerous intra-oral sites. Prominent findings include mucosal atrophy, salivary gland enlargement, recurrent parotitis, reduced flow rate, increased caries incidence and enhanced frequency of oral candidiasis. In the dry mouth, candidiasis may present in several forms, including pseudomembranous, chronic hyperplastic, chronic erythematous and angular cheilitis. Candidiasis management may include topical agents, such as nystatin, clotrimazole and ketoconazole, as well as systemic imidazole antifungals. Recent studies have identified a potential role for the aquaporin family of water channel proteins in the pathogenesis of SS. Aquaporins, which have been shown to be abnormally distributed in the glands of SS patients, translocate to the apical membrane upon M3 receptor activation and Ca^{2+}-mediated signaling. Thus, suppression of water secretion may be, in part, due to interference by autoantibody. By stimulating M3 receptors, cevemiline and pilocarpine increases salivary flow despite immune-mediated abnormalities in M3-receptor activation.

SS: the big questions

Philip C Fox, DDS, Carolinas Medical Center, NC, USA, spoke on a number of issues associated with SS.

Diagnosis of SS

The American–European Consensus Criteria help clarify the most important elements of SS. These criteria are composed of six domains: symptoms of dry eye, symptoms of dry mouth, signs of dry eye, signs of oral dryness, serum antibodies to SS-A and/or SS-B and a positive salivary gland biopsy. To meet classification criteria, four criteria must be present and must include either a positive antibody or biopsy. As these are classification criteria, it is possible to have SS and not meet the criteria.

Biopsy negative SS

Owing to sampling issues and the heterogeneity of lymphocytic infiltration, it is possible to have SS with a negative labial minor salivary gland biopsy. In order to meet criteria, a patient would be required to have anti-SS-A or -B antibodies.

Inheritance of SS

The genetics of autoimmunity in general is complex. SS is likely to be a polygenic disorder with multiple alleles contributing to susceptibility. Family members have an increased chance of having some autoimmune disorder (Sjögren's – rarely – or others). Genetics is only one factor contributing to the pathogenesis of SS.

What is the likelihood for any particular symptom to be secondary to SS?

Since SS may have a heterogeneous multisystem presentation, physicians and patients must be aware that glandular

(dry eye and dry mouth) and extraglandular symptoms (joint pain, fatigue, neuropathy and cough) may be caused by SS. On the other hand, patients with established disease should be aware that not every new symptom is attributable to SS and should be reported to their physician and investigated if necessary.

Risk of lymphoma & mortality from SS

It is definite that there an increased risk of developing lymphoma in the context of chronic SS. Markers are being developed (vasculitis, salivary enlargement, monoclonal protein and low C4) that will identify patients who are at relatively greater risk for lymphoma development. Nonetheless, aside from lymphoma, most studies show that overall mortality for SS patients (as measured by standardized incidence ratio) does not exceed that of the control population. Thus, SS is usually not life threatening – it is more life altering.

Are there effective treatments for SS?

Treatment of SS is multifaceted and is directed toward management of symptoms (artificial tears and salivas, sugar-free gums and systemic secretagogues, including cevemiline and pilocarpine); minimizing end-organ damage (fluoride treatment, remineralizing solutions, topical ocular anti-inflammatories such as cyclosporine drops, and oral antifungals) and control of underlying autoimmune mechanisms (hydroxychloroquine and prednisone when necessary).

What is the status of research?

Recently, the research outlook has dramtically improved. Funding for an US$11.5 million international registry for SS (SICCA) has been provided by the NIH in addition to awarding nine individual research grants totaling $3.5 million under a request for applications specific for SS. In 2007, the SS Foundation has awarded one Innovative Concept Research Grant, four Research Grants and three Student Fellowships. Active areas of investigation in Sjögren's research include: the genetics of Sjögren's, immunological mechanisms of disease, identification of outcome measures and biomarkers and exploration of new biological therapeutic approaches including B-cell targeted therapies.

Characterization of brain areas innervating salivary & lacrimal glands.

Cristian A Perez, The Rockefeller University, NY, USA, SS Foundation Research Grant Award Recipient, presented on the characterization of brain areas innervating salivary and lacrimal glands. Neurological control of glandular secretion originates in the brain. Identification of neuronal circuits innervating moisture glands should provide essential information about physiological mechanisms that control their function. Identification of neuronal types and characterization of their molecular repertoire could lead to identification of pharmacological targets involved in the modulation of saliva and tear production by residual glandular tissue. Murine experiments were performed using neuronal pseudorabies virus-tracing techniques. This allows tracing of single neuron pathways from the brain to the salivary and lacrimal gland. Molecular markers characteristic of neuronal subtypes were localized using green fluorescent protein-labeled transgenes. Multiple putative moisture gland control centers (MGCC) were identified in the cortex, amygdala, thalamus, hypothalamus and brainstem. A total of 48 MGCCs traced to lacrimal glands while 38 innervated salivary glands. A total of 11 MGCC were common to both pathways. Further characterization of neurons will hopefully lead to pharmacological targets for moisture stimulation in SS.

Impact of stress on autoimmune disease

Esther M Sternberg, NIH, MD, USA, spoke on the impact of stress on autoimmune disease. The immune system signals to the nervous system by many routes. Neuronal cell death and survival affect memory, cognition and mood. Cytokines released during inflammation result in a stress response inducing sickness behavior, fever and sleep. Cytokines may activate the brain via leaky areas in the blood–brain barrier, active transport mechanisms and through second messengers such as eicosanoids and nitric oxide species. Central negative feedback mechanisms aid in the attenuation of the inflammatory response via hypothalamic release of adrenocorticotropic hormone and the subsequent production of cortisol. Selye described stress as a nonspecific response of the body to any demand. Stressors can include psychological (performance, hierarchy, relationships and loss), physical (pain and exercise) and physiological (infection, disease, hemorrhage, sleep deprivation, etc.). Stress signals are received in the brain where they feed into the final common pathways of the stress response. This pathway is composed of brain hormones (the hypothalamic–pituitary–adrenal [HPA] axis) and nerve pathways (the sympathetic nervous system), which together coordinate the fight or flight response. Some degree of stress appears necessary to achieve optimal performance, whereas excessive stress is detrimental to the organism. Some aspects of our response to stress may be controlled by learning processes. Some of these processes include training and practice, biofeedback, stress-reduction programs, meditation/yoga/prayer, psychotherapy, exercise, social support and lifestyle change. Excessive stress has been linked to a predisposition to illness. By activating the HPA axis, the usual brain stress response results in the production of corticosteroids, thus suppressing the inflammatory response. Therefore, in the presence of excess stress, the ability to fight infection may be impaired. Stress situations that have been documented in the literature to be associated with impaired health include stress in chronic care givers, marital stress, student exam stress and stress induced by extreme military exercise. A blunted hormonal stress response mediated by genetic, surgical and pharmacological mechanisms may lead to impaired suppression of inflammation and a

predisposition to autoimmune disorders. In addition, resistance to the action of glucocorticoid hormones via receptor malfunction may similarly lead to autoimmunity. Several autoimmune and/or inflammatory diseases, including RA, SLE and SLE nephritis, have been associated with polymorphisms and/or mutations in the glucocorticoid receptor (GR). Alterations in GR number have been found in patients with SLE nephritis and Crohn's disease. Patients with SLE and Crohn's have also demonstrated increases in GR-associated proteins; in these instances the multidrug resistance glycoprotein and cortisol binding globulin, respectively. Finally, decreased glucocorticoid sensitivity has been shown in asthma and multiple sclerosis. It is likely that multiple factors predispose to alterations in the immune response associated with stress. Understanding interactions between the nervous system and the immune system may lead to future treatments for stroke, neurodegenerative disease and pain and inflammatory arthritis. Understanding how emotion affects health helps healthcare professionals respect and assist patients judicious use of complementary and alternative therapies and integrate care.

Gynecological Issues & SS

Gynecological issues and SS were discussed by Pamela Stratton, NIH, MD, USA. Studies examining pregnancy outcome in women with primary SS may be limited owing to the relatively late age of onset of SS. Many pregnancies reported in studies occurred prior to the diagnosis of SS. Nonetheless, limited data are available from several investigators representing diverse demographic populations. Overall, fertility rates, number of pregnancies, full-term births and premature births were similar between women with primary SS and controls. Compared with women with SLE, there was a lower risk of intrauterine growth retardation. As expected, women with primary SS had a greater frequency of infants with congenital heart block. Dyspareunia, most likely secondary to vaginal dryness, is the most common gynecological manifestation of SS. Symptoms of vaginal dryness appear to be secondary to inflammation and atrophy of vestibular glands. One study reports vaginal dryness occurring under the age of 40 years in three-quarters of women with SS. Occasionally, dyspareunia has been the presenting symptom of SS. Post-menopausal SS patients appear to be at the highest risk for dyspareunia when compared with premenopausal SS patients and postmenopausal controls. Urinary tract symptoms are generally more frequent and more severe in women with SS. Pelvic pain and urinary retention are prevalent symptoms in this population, whereas urgency and stress-incontinence are less common. Genitourinary symptoms have an adverse impact on quality of life for women with SS. Women with vaginal dryness had lower scores for social functioning and general health. Similarly, women with extraglandular involvement display reduced vitality, social functioning and general health.

Urological manifestations of SS

Urological manifestations of SS were discussed by Kristene E Whitmore, Drexel University College of Medicine, PA, USA. The incidence of interstitial cystitis is approximately 10-times greater among people with SS compared with the general population. Both disorders share similarities, including high prevalence, long delays in diagnosis, the presence of anti-M3 muscarinic antibodies in the blood and infiltration of target organs by $CD4^+$ lymphocytes. Typical signs and symptoms include urinary frequency and chronic pelvic pain or dyspareunia for more than 3 months. Diagnostic assessment requires maintenance of a voiding log, examination to identify or exclude associated causes of pelvic floor dysfunction and diagnostic tests including, but not limited to, urinalysis/cultures and cystoscopy. Treatments are individualized for every patient and employ a multidisciplinary approach with behavioral/physical therapy, pelvic massage, biofeedback, trigger-point injections, nerve blocks, oral or intravesical pharmacotherapy and sacral neurostimulation with implants.

David Bianchi, Uniformed University of the Health Sciences and George Washington University, WA, USA, spoke on ear, nose and sinus issues. The ear, nose and throat (ENT) manifestations of SS are common and affect virtually any part of these organs. Clinicians are often challenged to distinguish between manifestations of SS and other conditions (e.g., allergies or infections) that cause overlapping signs and symptoms. Otologic manifestations of SS may include itching and scaling of the outer canal, eustachian tube dysfunction, otitis media, hearing loss or balance problems. The most common nasal problems include chronic rhinitis and recurrent sinusitis. The diagnostic approach in all patient groups is similar and includes a thorough ENT evaluation, including nasal endoscopy, cultures and imaging studies (e.g., CT scan of the sinuses) when appropriate. In SS, however, the therapeutic approach is different. Local nasal sprays (corticosteroid and decongestant) are preferred treatments as compared with oral antihistamines/decongestants in order to prevent exacerbation of systemic dryness. A greater emphasis is also placed on the use of nasal irrigation with saline/bicarbonate solution, use of nasal emollients, humidifiers and air purifiers to treat ENT problems in SS patients.

Understanding blood changes in SS

Herbert SB Baraf, George Washington University, WA, USA, presented a talk on understanding blood changes in SS. Laboratory evaluation of SS is important to confirm or establish the diagnosis, determine if SS is primary or secondary, monitor the disease course, determine the risk of lymphoma and monitor medication safety. Therefore, common laboratory tests (complete blood counts, chemistries and urinalysis) are important to perform on a routine basis. Acute phase reactants are a group of proteins synthesized in the liver. The majority of commonly measured acute-phase reactants are the

sedimentation rate and the C-reactive protein. Acute-phase proteins are produced in excess in response to any bodily injury (inflammation, infection, trauma and so on). Thus, acute-phase reactants are never specific nor diagnostic for any given disorder, including SS. Nonetheless, they are sometimes useful to monitor disease activity. β-2 microglobulin is a protein that is found on the surface of lymphocytes that may be elevated in serum in autoimmune disorders, including SS. High concentrations have been found in the tears and saliva in SS. β-2 microglobulin has been variably utilized to monitor disease activity in SS. Cryoglobulins are immunoglobulins (antibodies) that form solid percipitates in the cold. In Sjögren's, they have an enhanced association with Raynaud's phenomenon and with vasculitis. Their presence may also indicate the development of a certain form of lymphoma. Tests such as serum protein electrophoresis and immunoelectrophoresis have the ability to identify monoclonal immunoglobulins, which are sometimes indicative of lymphoma development. Decreasing levels of the complement component C4 may also confer an increased risk for lymphoma. Autoantibodies are the hallmark of Sjögren's syndrome in the blood. Important autoantibodies include rheumatoid factor (RF), antinuclear antibodies (ANA) and the more specific ANA subset anti-SS-A and -B. RF is most often used as a screening test for RA, but it is not specific for RA and is seen in a number of other autoimmune disorders, including SS where it may be present in up to two-thirds to three-quarters of patients. In the absence of RA, a positive RF test is not diagostic for SS. Similarly, ANA is primarily used to screen for lupus (SLE) but may be observed in up to three-quarters of SS patients. The ANA subset of anti-SS-A and SS-B was first described in the serum of a Sjögren's patient and is frequently utilized in the work-up for SS. A speckeled pattern on an ANA test is frequently caused by antibodies to SS-A and/or -B. Approximately 70% of SS patients are anti-SS-A positive and approximately 30–40% are anti-SS-B positive.

Celiac disease & its association with other autoimmune disorders

Allessio Fasano, University of Maryland, MD, USA, presented an overview of celiac disease and its relationship to autoimmune disorders. Our understanding of the relationship of celiac disease to other autoimmune disorders is evolving. Celiac disease is unique in that the environmental trigger (gluten), autoantigen (tissue transglutaminase) and disease susceptibility genes (*HLA-DQ 2* and *DQ-8*) are all known. Celiac disease affects virtually every racial and ethnic group and approximately 50% of cases are latent. It occurs in 2–15% of patients with SS. Celiac disease is now typically diagnosed in older children and adults but may present at any age (from infancy to 92 years of age). Presenting manifestations include iron-resistant iron-deficiency anemia (most common), dermatitis herpetiformis, osteoporosis, short stature, delayed puberty, diarrhea, hepatitis, arthritis and epilepsy. Celiac disease is diagnosed by serologic tests (IgA anti-endomyseal and antitissue transglutaminase antibodies) or small bowel biopsy. Additionally, *HLA-DQ2/DQ8* negativity can exclude the diagnosis with 99% certainty. Recent studies suggest that the prevalence of other autoimmune disorders in celiac disease may be related to the duration of gluten exposure. Early diagnosis and strict adherence to a gluten-free diet may completely reverse the disease and potentially prevent other complications.

Future treatments for SS: looking into the crystal ball

Finally, Frederick B Vivino, University of Pennsylvania School of Medicine, PA, USA, spoke on the future of SS treatments. The future of treatment for SS looks bright. Current therapeutic strategies include B-cell depletion, interference with T-cell activation or migration to sites of inflammation and anticytokine therapy. A variety of agents either US FDA approved or under study for closely related disorders, such as RA, SLE or multiple sclerosis, could also be potentially useful in SS. Two randomized, placebo-controlled clinical trials for rituximab (anti-CD20), a B-cell-depleting agent approved by the FDA for the treatment of RA, are currently underway in Europe. A fully humanized version of anti-CD20 (ocrelizumab) and another B-cell depleting antibody (epratuzamab; anti-CD22) are also in trials for RA and SLE, respectively. Abatacept (CTLA4-Ig) is FDA approved for RA patients who fail with TNF-α inhibitors and could be of benefit (it works by T-cell costimulation blockade) in SS. The psoriasis drug (efalizumab, anti-CD11a) functions by inhibiting T-cell migration to inflammatory sites and is currently in Phase II clinical trials at the NIH for SS. Fingolimod (FTY-720) is an oral immunomodulating compound in Phase II clinical trials for MS that downregulates the S1P1 receptor on activated lymphocytes, thereby trapping them in lymph nodes to prevent trafficking to target organs. Promising anticytokine therapies include anti-IL 6 and anti-Blys (belimumab), both of which are in Phase II–III clinical trials for RA and lupus but are likely to be studied in SS as well. In the future, gene therapy and/or stem cell research may provide novel approaches to regenerating exocrine glands or resetting the immune system toward a normal balance; however, no clinical trials in humans are currently planned.

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Dr Steven Carsons is a consultant and speaker for Daiichi Pharmaceuticals.

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