Meeting Report: Sjogren’s syndrome at the American College of Rheumatology in San Diego, CA from October 25-28, 2013

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Summary

From October 25-30th, 2013, the American College of Rheumatology (ACR) was held in San Diego, CA. Over 10,000 participants from 5 continents came to present papers on pathogenesis and therapy. This review will focus on presentations regarding classification, pathogenesis and therapy of Sjogren’s syndrome (SS).

The accepted abstracts from the 2013 meeting are available online (www.acrannualmeeting.org) and can be viewed by choosing “view abstracts” option. In this article, I will review presentations that have a particular interest in clinical practice and pathogenesis.

In terms of clinical classification criteria, the confusion between the American-European Consensus Criteria (AECOG)¹ used in Europe and the recently proposed SICCA criteria² continues. It is clear that about 90% of patients fulfill both criteria. However, the main measure of disease activity, the European Sjogren’s Disease Activity Index (ESSDAI) was based on serial evaluation of patients who fulfilled the AECOG³. The key problem is that the ESSDAI, used in clinical trials, may be significantly altered due to the 10% of discordant patients⁴,⁵.

From recent publications and discussions at ACR in the SS symposium, it is clear that an independent cohort has not validated the SICCA criteria and this was a requirement before their acceptance by ACR. Further, shortcomings in the SICCA criteria discussed at the meeting indicate that significant changes in this criteria will be required before it should be submitted for validation⁶,⁷. Despite these shortcomings in the SICCA criteria and their lack of required validation (which was stipulated as a “preliminary endorsement” by ACR), the SICCA criteria have been published on ACR website as the “gold standard” and leaving rheumatologists and pharmaceutical issue in a quandary.
Among the more pleasant parts of the ACR meeting regarding SS, genome wide sequencing (described below) now have identified one genetic loci (the homing receptor CXCR5) that distinguishes SS from SLE (Sivic, OK)\(^8,9\). This helps explain the tissue specificity of SS since it encodes a tissue preferential homing receptor known to be expressed on salivary and lacrimal glands. Another exciting report was the finding of the PX27 receptor which yields a gain in function that may play a role in SS\(^10\).

A separate group detected a germ line mutation in the A20 gene (a member of TNF family that controls NFkB activity) (Xavier, Paris)\(^11\) that was found in SS patients with mucosal associated MALT lymphoma. This helps explain the higher tendency of SS lymphocytes, under the action of B-cell stimulatory factors, to undergo lepromatous change.

Gottenberg (France, #1488) showed that gene expression profile did change in the ASSESS cohort, where therapy was assessed by ESSDAI measurement. The changes in interferon type 1 were not tightly correlated to the clinical parameters, suggesting that current therapies are still missing part of the pathogenetic process.

Although we did not see breakthroughs in new therapy presented at the ACR meeting, these basic science studies certainly suggest promising new targets. Of most importance, the pharmaceutical industry is now taking an interest in SS and more trials are being launched.

Background

There has been a steady growth in the number of abstracts and sessions devoted to Sjogren’s syndrome (SS) over the past decade of ACR meetings. It was also encouraging that many pharmaceutical companies are now expressing interest in SS as a target. This dearth of effective therapies for systemic manifestations of SS contrasts with the large number of therapies for rheumatoid arthritis and studies for psoriatic arthritis. Even multiple sclerosis and fibromyalgia have seen
a number of approved therapies. SS shares the undesirable “distinction,” along with scleroderma, of still being at the stage of exploration of targets. But at least now we are seeing new targets in both SS and scleroderma, as genome wide screens that suggests potential targets.

Specific sessions were devoted to Disease Classification Criteria, Genetics, Pathogenesis and Cytokines, and related diseases such as IgG4 related disease (including Mickulicz syndrome).

III. Classification Criteria

At sessions sponsored by the Sjogren’s syndrome Foundation (SSF), the confusion over the current criteria for diagnosis continues to be debated. The Consensus American-European Criteria (AECG)(Vitali Italy), and The SICCA criteria (Shiboski, USA), were compared. Both sets of criteria are quite similar with about 90% concordance. However, the 10% of patients that fulfill one set of criteria (but not the others) could influence the outcome of clinical studies.

The most important “child” of the AECG criteria been the “European Sjogren disease activity index (called ESSDAI)(Seror, France). Over 1300 studies and well defined cohorts in Europe have been to study natural history, prognosis and response to therapies. Although the two sets of criteria are 90% similar, the results of the study would be altered if a difference entry criteria (SICCA rather than AECOG) were used.

The AECG criteria have become known to clinicians, pharmaceutical, and regulatory agencies as validated endpoints for studies. Although it was clear that certain shortcomings (such as the use of Rose Bengal and the exclusion of IgG4 related disease) that were present in AECG’s original form, these modifications for multiple clinical trials during the past decade have easily been accomplished by selection of inclusion and exclusion criteria.

The SICCA cohort is an NIH-funded international registry initially suggested in San Francisco (Daniels, CA; Shiboski, CA) and
subsequently in five academically based research groups located in Argentina, China, Denmark, and Japan under the direction of University of California San Francisco. Subsequently, three groups from the United States (Johns Hopkins and University of Pennsylvania) joined in 2009.

The question under discussion was whether the proposed SICCA criteria would improve the uniformity of patients enrolled for clinical trials. The SICCA criteria differ from the 2002 AECG criteria in three ways: they include no subjective ocular and oral symptoms and no functional or morphological tests for the salivary glands, they use a new ocular staining score (OSS) as the only criterion for ocular involvement, and they allow the use of an antinuclear antibody (ANA) titer $\geq 1:320$ plus rheumatoid factor (RF) positivity as an alternative to anti-SSA/SSB antibody positivity for the assessment of systemic autoimmunity.

Reports from several cohorts that compared SICCA and AECG classification have recently been published and their results were further discussed at the meeting. These included the Oklahoma cohort (Scoffield, USA), the Scandinavian cohort (Jonsson, Norway), the French Brest Cohort (Devic, France) and the Japanese cohort (Sumida, Japan). In particular, the use of unstimulated saliva flow in AECG (not required in SICCA) helped with specificity of diagnosis of SS. Also, the finding of low Schirmer test (AECG) did not closely correlate with ocular staining score $>3$ (SICCA) and contributed to differences between classification criteria. Although small in number, the patients who are discordant in the two criteria may lead to confusion in classification since currently used endpoints (such as the ESSDAI) for clinical studies have been based on the AECG.

Several conclusions derived from these discussions.

- The SICCA criteria have been called the ACR criteria since it was granted “ACR” recognition contingent upon validation by an independent cohort. Xavier (Paris), the site chosen for the external validation, announced that the grant proposal to support this validation was not approved and thus no validation is on the immediate horizon. Since this validation has not been performed and the European participants (Jonsson, Norway;
Cornec, France; Vitali, Italy) indicated that the criteria should still be referred to as the SICCA criteria (not the ACR criteria).

- According to all participants, significant changes in the SICCA criteria will be required before it is ready for its required validation. The SICCA criteria are now listed on the ACR website with implication that they are the only acceptable criteria even though they have not been validated and will require modification. Although it sounds like a trivial semantic issue, there are already reports of research grants and treatment protocols using the AECG criteria being “rejected.” For not using the SICCA criteria.

- For the present time, we should enroll patients that fulfill both AECG and SICCA criteria for clinical studies. This is important since both clinicians and regulatory agencies have familiarity with AECG criteria and the ESSDAI method of assessing extraglandular activity.

- All participants agreed that there is a pressing need to overcome the current differences in diagnostic criteria that are generating unnecessary diversion from our real task of developing effective therapy.

III. Diagnostic Methods

One of the most important presentations was the value of salivary gland ultrasound, performed by experts, to improve the sensitivity and specificity of both the AECG and SICCA criteria (Cornec, Brest #507).

The correlation of ultrasound and histopathologic changes on biopsies remains unclear (Germano and Jonsson, Norway, #208). One of the key issues is the lack of standardization and inter-observer variation even among expert ultrasonography (Jousse-Joulin, France, #508). This variability even among experts provides a cautionary note as rheumatologists in the US rush to have “office” ultrasound machines (Costa, France #510).

One of the main findings on ultrasound is hypo-echogenicity in SS and this would be presumed to result from scar tissue, but this histologic finding has not been reported in either initial or repeats
biopsies from SS patients (Cornec, France, #507). This may reflect the usual site of biopsy is a minor salivary gland, while ultrasound are done on major salivary glands (Nicoletta, Italy, #850). There are studies of histology of parotid biopsies from SS patients and clinical correlations by Pipje and co-workers (Amsterdam)\(^{16-20}\). It will be important to perform ultrasound on the major glands of these SS patients in the Netherlands, since parotid biopsies are not done by ENT surgeons in other countries or other countries, perhaps due to medical-legal concerns of potential fistulas from the parotid biopsy.

Different methods of antibody detection may yield conflicting results. Although the antigen termed “SS-A” is frequently considered as a single molecule, it is historically composed of two molecules termed Ro-60 and Ro-52. These two molecules are “blended” in commercial assays and may lead to different results (Baer, Baltimore #515).

Herold (#106) pointed out that not all patients with a positive ANA have an associated autoimmune disease and that a frequent cause of “misdiagnosis” of a positive ANA is antibody to dense fine speckle 70 kd antigen (DFS70/LEDG). The positive immune fluorescence was confirmed by immunoprecipitation and ouchterlony results. Of importance, almost 9% of “clinically normal individuals” referred to rheumatology clinic because of a positive ANA had a DFS70 pattern chromatin binding protein (termed LEDG)\(^{21}\). Thus, there is actually a negative correlation of anti-DFS70 antibody with development of either SS or SLE\(^{22}\). This is important since a large proportion of patients referred to rheumatologists have only symptoms of fibromyalgia and a positive ANA. Recognition of this subset may save both time and money for the health care system.

III. Clinical Manifestations

Although the genetics of different SS groups show differences (discussed below), the clinical manifestations in cohorts in the US, Europe, China and Japan are remarkably similar (Tsumida, Japan; Shiboski, US; Jonsson, Norway; Scoffield, OK). The ESSDAI contains 12 domains that cover skin, lung, arthritis, neuropathy, and laboratory abnormalities and Japanese patients exhibited similar clinical manifestations in each domain\(^3\).
However, it was surprising that the frequency of extraglandular manifestations, as measured by ESSDAI were higher among Japanese patients in Japan (Tsumida, Japan) than in American Japanese. Also, a lower ESSDAI was reported among SS patients of African descendent (Shiboski, San Francisco). This seemed contrary to our prior expectation of a lower ESSDAI score among a society that had a large vegetarian or fish intake, as well as a national health care system for early diagnosis. Similarly, severity of SLE among African Americans has been reported as significantly more severe.

A major difference in frequency of extraglandular symptoms may reflect ascertainment bias in the “enrollment of patients”. In Japan, China and India (Agarwal, India; Li, Beijing), patients are first seen in primary medical care clinic and signs/symptoms such as rash, neuropathy, or major laboratory abnormalities are detected. These Japanese or Chinese patients are then referred to rheumatology clinic where laboratory studies such as antibody to SS-A and lip biopsy are first ordered and indicate SS as the cause for the clinical manifestation.

This “ascertainment bias” of using clinical symptoms to document a clinical presentation is obvious in retrospect In the US, patients are more frequently screened for vague symptoms of fatigue with an ANA panel and the finding of a positive serology leads to rheumatology evaluation.

IV. Treatment

Abatacept reduced disease activity in early primary SS in a phase II open label study (Vissink, Netherlands #522). Patients with disease duration less than 5 years and DMARD naive were enrolled. Abatacept was well tolerated and showed significant decrease in ESSDAI. However, the clinical trials of abatacept in SLE were terminated due to safety concerns (Van Vollenhoven, Netherlands, #1607).

Seror (Paris, #511) reported an improved pattern of lymphocyte infiltrates on serial lip biopsy in 2 small European trials of belimumab (The Beliss Study). Among 15 treated patients, the ESSDAI and BAFF levels showed significant improvement. As this was not
placebo controlled, it is difficult to establish clinical efficacy. Levels of endothelial growth factor were decreased in the belimumab treated patients (Bobic, Greece #105). However, the most interesting part of the discussion was that patients showed relatively less subjective improvement in their ocular and oral symptoms than would be expected from their improvement. This suggests that we may improve “peripheral” extraglandular manifestations but are still missing a key element of SS that regulates pain, myalgia and fatigue.

A review of biologics in the European registry for SS during the past 2 years indicated that the most frequently used agent was rituximab (van Vollenhoven, Netherlands #1585). Jousse (France, #2881) reported an improvement in ultrasound of the salivary glands in the TEAR and Tractis studies (both small studies that use a placebo control) conducted in both UK and France. However, corresponding changes in lip biopsy were not observed. Discussion of this interesting paper indicated that most rheumatologists were using rituximab for specific flares such as vasculitis including mixed cryoglobulinemia, hematopoetic changes (such as hemolytic anemia or thrombocytopenia) or parotid gland swelling on an “as needed” basis rather than on a continuing basis.

Vitale (Italy, SS workshop) reviewed promising agents in pre-clinical development for SS or SLE, including anti-CD22 (Epruzatumab), bambercept, aticicept (anti TACI) anti-IL6 (tocilizumab), anti-IL10, anti-IL17, anti-IFN type 1, and anti-C5a (eulizumab).

Traditional drugs including methotrexate (for arthritis), azathioprine (for nephritis) and mycophenolic acid to help taper steroid dose remain our standard of care (Vitali, Sjogren’s Syndrome Symposium). Other trials currently in progress low dose cyclosporine with hopes of finding a dose that is efficacious but not renal toxic (clinicaltrials.gov).

Gottenberg (France, #1432) reported the rate of serious infections remains stable in patients with multiple retreatments based on the rituximab (AIR) registry. Although over 60% of patients sustained a serious infection, they continued to receive rituximab when their systemic manifestations required treatment. About 5% of patients had serious AE after the first cycle and similar percentage after subsequent trials including a cohort with 5 cycles. This points to the
fact that we have a long way to go with treatment of systemic autoimmune features.

In summary, there is a great deal of interest by pharma in SS and that is encouraging. However, the current results have limited benefit on the “benign” symptoms (fatigue, myalgia, cognitive) that patients most consider limitations to their quality of life. Symptomatic therapies remain largely unchanged over the past decade.

III. Genetics

Three extensive genome wide screens were discussed. The Oklahoma cohort (Lessard, OK #2770), the SICCA cohort (Criswell, USA, Sjogren’s symposium) and the Chinese SS cohort. For simplicity, the results of the Oklahoma GWAS will be detailed below as they were recently published in Nature Genetics.

Lessard #2770 reported HLA related genotypic data on 1638 patients in a genome-wide association study (GWAS). The strongest effect in GWAS was the long known and strong association with HLA allele association. Ancestral haplotype of DRB1*0201, DQB1*0201, and DQA1*0501. However, the recognition of RFX5, a key transcriptional regulator of the HLA class II loci and I extended previous HLA association.

In addition to the HLA data from GWAS, C.Lessard and K. Sivis (who is known in prior literature by her maiden name Kathy Moser) presented additional exciting data in the SS symposium. Other statistically significant loci that are involved in both innate and adaptive immunity in Sjögren’s syndrome included:

- **IRF5** - RF5 is a member of the interferon regulatory factor (IRF) family, a group of transcription factors with diverse roles, including virus-mediated activation of interferon, and modulation of cell growth, differentiation, apoptosis, and immune system activity.
- **STAT4** - STAT4 genes lie next to STAT1 gene locus
suggesting that the genes arose by gene duplication. STAT proteins have several functional domains, including an N-terminal interaction domain, a central DNA-binding domain, an SH2 domain, and the C-terminal Tran activation domain.

- **IL12A** - Two chains of the IL-12 receptor form heterodimer after IL-12 binding and activate the receptor associated JAK kinases, termed JAK2 and TYK2. Stat4 is phosphorylated by these tyrosine kinases, homodimerizes via its SH2 domain and translocates into nucleus to activate gene transcription.

- **BLK** - Tyrosine-protein kinase also known as B lymphocyte kinase.

- **TNIP1** - TNIP1 has been shown to interact with TNFAIP3 and MAPK that are both rapidly induced by TNF and inhibit NF-kappa B activation as well as TNF-mediated apoptosis. Knockout studies of a similar gene in mice suggested that this gene is critical for limiting inflammation by terminating TNF-induced NF-kappa B responses.

- **CXCR5** - also known as or Burkitt lymphoma receptor 1 (BLR1). CXCR5 gene is specifically expressed in follicles in lymph nodes. The gene plays an essential role in B cell migration.

These results highlight the importance of genes that promote innate immunity (type 1 interferon signature) and acquired immunity (HLA linked recognition of antigen by T-cells and B-cells through traditional antigen presenting pathways. One interesting observation is the CXCR5, a homing receptor, was not found in GWAS of SLE patients. This is one of the few examples where SLE and SS can be differentiated and helps explain the relative organ specificity and lymphoproliferative nature of SS.

Although genetic associations have been noted above, the majority is not located in protein coding regions of the genome. Adriano (OK, #1489) presented data to suggest that these non-protein coding RNA sequences may act as distant promoters or perhaps acting as “scaffolding” to held direct other proteins in their activity. Other newly identified genetic loci include OAS1 that may promote a splicing change to the p46 variant of an interferon inducible gene (Li, OK #2772).
The increased frequency of non-Hodgkin’s lymphoma in SS may be linked to a genetic polymorphism known as A20 (Xavier, France in the SS symposium), which regulates NFK-b activity. These exciting results that link MALT lymphomas in SS patients to other non-SS patients with MALT lymphoma were recently published.

Finally, the recent report of genome wide screening in Han Chinese has confirmed the different HLA-DR association and identified new loci termed GFT1. This study also points out other different genetic loci and points out the diversity of factors that can contribute when a disease such as SS develop in different ancestral and ethnic backgrounds\(^{23,24}\).

Although I have placed great emphasis on GWAS, it is only fair to reflect that skepticism is still indicated in using this approach as a tool for translation into clinical therapies in multigene diseases such as SS\(^{25}\). As expressed in a recent Nature Genetics review, this scepticism arises from such aspects as the large number of genes involved in autoimmune diseases such as SS and the large number of alleles at each gene. For truly significant predictive capacity, we require sample sizes much greater than currently available\(^{26}\).

Pathogenesis

An important finding by Lessard (OK, #) was the influence of RX5 loci that may help explain the very high genetic linkage with HLA-DR. This polymorphic snp does not correspond to a functional protein and make act as a different promoter or a non-coding RNA. Given the importance of acquired immune responses (including characteristic autoantibody and T-cell subsets), an entirely new avenue of treatment may be possible.

The linkage of innate and acquired immune system may be provided by the NK like cells (Nocturne, France #2771). In particular, a specific
protein NCR3/NKp30 was released by NK cell degranulation that facilitates cross talk between NK and dendritic cells to regulate interferon g secretion. This factor may help explain a role for Th17 cells in the SS gland and provide a novel series of therapeutic targets.

Novel microRNA’s, including 44 highly expressed candidates, were found in minor salivary gland biopsies of SS patients (Gallo, #1491) that may influence transcription of lymphocytes within the salivary gland. Differences in gene modification such as histone acetylation were also detected in the SS salivary glands and associated changes in histone deacetylasse 1 (but not acetylase 2)(Guo, #1492).

Alterations in salivary gland cytokines (IL-21 and IL-33) were found associated with germinal center formation (Jung #1494)(Bombrdieri #1495). The presence of germinal centers has previously been shown to correlate with disease severity (extraglandular manifestations) and lymphomagenesis.

VI Conclusion

In my opinion, the most exciting highlights of this year’s ACR highlights for SS were in the field of genetics. We obtained genetic confirmation of our hypothesis that both innate and acquired immune systems were involved. NK cells may provide a link between these two systems. A difference between SS and SLE was found in the GWAS (CXCR5) that makes clinical sense to explain the lymphoproliferative properties in SS that are not present in SLE.

References


