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American College of Rheumatology 67th Annual Scientific Meeting
Systemic Lupus Erythematosus and Sjögren's Syndrome CME

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Goal

The goal of this activity is to provide current information, define "state-of-the-art" treatment protocols, and describe clinical strategies for the management of rheumatic diseases in selected areas.

Overall Learning Objectives

Upon completion of this activity, participants will be able to:

1. Identify current and upcoming treatments for the management of rheumatoid arthritis, the spondyloarthropathies (including psoriatic arthritis), and osteoarthritis.
2. Enumerate influential elements in the etiology of systemic lupus erythematosus and Sjögren's syndrome.
3. Identify possible new treatment strategies for systemic lupus erythematosus and Sjögren's syndrome.

Learning Objectives for this CME Activity

Upon completion of this activity, participants will be able to:

1. Enumerate influential elements in the etiology of systemic lupus erythematosus and Sjögren's syndrome.
2. Identify possible new treatment strategies for systemic lupus erythematosus and Sjögren's syndrome.
3. Describe mechanisms that may play a role in the development of systemic lupus erythematosus and Sjögren's syndrome.

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Contents of This CME Activity

Update on Systemic Lupus Erythematosus

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Introduction

New information on systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) was presented in over 400 presentations based on submitted abstracts and an additional 15 State-of-the-Art presentations dealing with preclinical and clinical features. Particular clinical highlights in SLE included a new multicenter trial indicating that mycophenolate mofetil (MMF) might be used for the induction of patients with severe SLE membranoproliferative nephritis instead of our traditional intravenous cyclophosphamide (IVC). As discussed below, this study led to heated debate about study design and short period of follow-up. Also, disappointing results in SLE with monoclonal antibodies to tumor necrosis factor (TNF) in comparison to the dramatic responses that have revolutionized our therapy of RA were discussed. In SS, the failure of TNF inhibitors was reported in large multicenter trials in contrast to a smaller open-label trial previously published. The relative failure of these therapies led to more focused attention on B-cell biology. The basic research studies also focused on the results from genomic screening to identify candidate genes for therapy, and the interaction of B cells with antigen-presenting cells and T cells. The overall consensus was that the meeting was exciting, but that we are still at the early stages of using new strategies for therapy, such as B-cell depletion using anti-CD20 antibody and the blockage of molecules that facilitate B-cell activation such as Blys, a novel member of the TNF superfamily.

An overview of the basic science update for SLE during the past year was summarized in a series of State-of-the-Art Lectures. These presentations (described below) reviewed the wide gamut of candidate genes identified by microarray and proteomic assays, the cells that express these genes and the biology of cells/animals with either transfection or knockout of candidate genes. If last year's theme was the regulation of "innate" immunity that gives rise to TNF and the success of TNF inhibitors in rheumatoid arthritis, the overall theme this year was the disappointment of TNF inhibitors in SLE or SS that leads to a further understanding of B-cell biology. Although it is likely that TNF generation plays a necessary role, it is not sufficient to solely block this cytokine as a therapeutic goal. A combination of therapeutic approaches may be necessary. The epidemiology of both SLE and SS suggests an important interaction of environmental agents recognized by the innate immune system and Toll receptors and the genetic component, which is mediated by antigen presentation to T cells and B cells through a relevant series of cell membrane receptors, secondary signals, transcription factors, and cytokines/receptors that form an increasingly complicated series of interactions that can give rise to either stimulation or feedback inhibition. The overall theme continues to be the recognition that the same factors that promote innate and adaptive immune responses to pathogenetic microbes in healthy individuals lead to autoimmune diseases such as SLE or SS due to a genetic predisposition toward impeding clearance of cellular debris and promoting activation of the B-cell autoimmune process. These occur because of failure to deplete potential autoimmune cells at the level of peripheral tolerance. Perpetuation of the immune response by these cells then occurs, due to an increasingly large number of genetic polymorphisms involving regulatory factors, each of which makes a small contribution in a subset of individuals.

Immunologic Mechanisms

The basic mechanisms of immune cell tolerance were reviewed by Kotzin (Colorado),[1] Goldring (Massachusetts),[2] and Tsokos (Maryland),[3] while the dysregulation of B cells in autoimmunity was summarized by Shlomchik (Connecticut).[4] The failure to remove autoimmune cells in SLE patients does not appear to occur at the thymic level but predominantly at the level of peripheral removal. The latter process involves the interaction of nascent lymphocytes with homing receptors on high endothelial venules, costimulation by autoantigen by dendritic cells that activates a memory program rather than apoptosis, and presence of a tissue microenvironment that promotes cellular longevity rather than apoptosis.

In contrast to several years ago when the entire life span was interpreted in the context of the adaptive immune system (ie, HLA-linked antigen presentation), an important role for antigen recognition by the Toll receptors (ie, innate immune system) was summarized by Beutler (California)[5] as well as how the innate immune system serves to stimulate, perpetuate, and activate the acquired immune system. These Toll receptors were initially identified by their rapid response to lipopolysaccharide- and mannose-binding lectins, but the Toll family now has over 10 members that have both stimulatory and inhibitory actions. Each member of the Toll receptor family is encoded by a single gene and each recognizes a repetitive antigen, including the repetitive motif associated with bacterial infection (ie, lipopolysaccharide), as well as other environmental factors such as bacterial DNA motifs CpG and flagellin. Viral-encoded double-stranded RNA, long recognized as an inducer of interferons (IFN), is also recognized by additional Toll receptors. Also, products from apoptotic cells may stimulate these pathways.[6] Thus, on a mechanistic basis, it can be envisioned how environmental agents (ie, bacteria or viruses or mycobacteria) as well as cellular debris can initiate and perpetuate the acquired (adaptive) immune response in genetically predisposed individuals. These basic science studies have also suggested that interferon-type 1 may be a key link between the innate and acquired immune systems. As such, IFN

and their subsequent induced genes may serve as a new target in SLE and SS. Also, cell surface signals from the activated dendritic cells provide links to the adaptive immune system.[7]

The Interferons

More than 40 years ago, the interferons became the first cytokine family to be discovered. After initial enthusiasm as therapeutic agents or targets in autoimmune disease, they have languished for years until their recent "rediscovery." As soon as the alpha IFN region of the genome was cloned, it was recognized that IFNs comprise a complex set of gene products. With sequencing of the human genome, we know that type 1 IFN locus on chromosome 9p21 includes at least 13 alpha IFN isoforms as well as a single IFN-beta gene. Also, IFN-omega, IFN-kappa, and IFN-tau have been identified. In the field of microchip analysis for transcription and proteomics, a series of genes associated with type 1 and type 2 IFNs have been developed. For example, studies reported at this meeting used microchip analysis of messenger RNA to show that alpha IFN induction occurs early in the course of SLE and that the level of IFN-related transcripts increases with this disease activity and the level is suppressed by glucocorticoid treatment.[8]

The functions of all of the type 1 interferons are not yet understood but they appear to share a single receptor and knockout of this receptor in mice prevents SLE-like disease. There is a single type 2 interferon (previously known as interferon gamma) with its unique receptor. The type 2 IFN also plays a critical proinflammatory role and characterizes the pro-inflammatory CD4 T lymphocyte. Increasingly, it appears that type I IFN "sensitizes" T cells to activate their type 2 IFN programs. Indeed, gene expression by microarray methods of blood or tissues from SLE patients and tissues in animal models show that most of the upregulated genes in SLE patients can be related to type 1 or type 2 IFN stimulation. However, simple blockade of the IFN-type 1 receptor may lead to some unexpected consequences, since IFN-beta and -omega are known to contribute to normal antiviral defense, while IFN-tau plays a role in maintaining a normal pregnancy and perhaps other cell-cell interactions. The original description of alpha IFN in SLE as acid labile remains poorly understood, but may reflect an altered glycosylation state of 1 or more of the interferon isoforms.[9]

The plasmacytoid dendritic cell, a cell distinct from the well-known macrophage, appears to be a major source of interferon alpha. The plasmacytoid dendritic cell can differentiate from myeloid precursors[10] and SLE sera can promote this differentiation in vitro. Cell markers BDCA-2 and BDCA-4 identify the plasmacytoid dendritic cell. The BDCA-4 molecule is a receptor for lectins of the C-type, linking these cells to innate immune responses. Also, immune complexes containing nuclear material mediate further immune system activation in part by binding to Fc receptors that activate complement and bind to Fc receptors. Thus, the activation of the innate system in SLE patients via dendritic cells may occur through a variety of mechanisms.

The innate responses communicate with the acquired immune responses through IFNs and supplement the activation of the acquired responses that are also receiving restimulation from immune complexes that bind to Fc receptors and lead to subsequent antigen representation. In this manner, IFN appears to act as an adjuvant-like factor that promotes immune responses to self-antigens that may initiate and perpetuate the autoimmunity characteristic of SLE. Self-antigens derive from apoptotic cells and other sources generated in the normal course of events. However, defective clearance of this cellular debris in SLE or SS (called the garbage disposal hypothesis) is made more likely by complement deficiency or impaired processing of the breakdown process. The autoantigens are expressed on the surface of antigen-presenting cells in the presence of costimulatory molecules to trigger sustained activation of the self-reactive T cells and B cells, perhaps due to genetic factors that promote exaggerated responses or other molecules that fail to terminate these reactions.[11]

In addition to their actions on dendritic cells and T cells, IFN also enhances B cells' responses and promotes immunoglobulin isotype class switching, through its induction of IL-10, dendritic cell-mediated effects and possibly through direct effects on B cells. Increased immunoglobulin class switching contributes to production of pathogenic IgG and IgA autoantibodies. Alpha IFN also promotes Fas ligand expression on natural killer cells, augmenting their capacity to mediate target cell apoptosis. All of these factors favor T- and B-cell reactivity to self-antigens.[11]

Genes and the Environment

Many of the presentations focused on the interaction of genetic and environmental factors.[1,5] It has been proposed that, in genetically predisposed individuals, viral infections containing double-stranded RNA or bacterial infections with CpG-motif DNA may initiate the cascade via specific Toll receptors. In this regard, there is an intensive search for specific inhibitors of Toll receptors to serve as a new therapeutic modality. The story of the early stages of immune activation in SLE involving IFN, stimulating cofactors, and linkage of innate and adaptive immune systems continues at a rapid pace as an increasing number of second signals and transcription factors are identified. In animal models, novel

therapies to target plasmacytoid dendritic cells proved promising for SLE but also inhibited the normal response to herpes virus. Thus, the goal of therapy will be to selectively inhibit the components of the IFN pathway that contribute to disease, while leaving intact enough of the IFNs and their receptors to maintain effective defense against normal viral infections. The complex and partially redundant family of IFN molecules, as well as the heterogeneity of the SLE patients, will make this a formidable challenge.

Kotzin (Colorado)[1] reviewed the multiple genes associated with self-reactive immunity. Although the most important still map to the major histocompatibility gene, multiple other genes play a role. The extent of the genetic effect is shown by the familial aggregation and the concordance among identical twins (about 25%). Other genes that play a role include those involved in T-cell activation (TGF-beta receptor, programmed cell death genes) and B-cell activation (Fc-gamma receptor types II and III). It appears that Fc-gamma receptor II polymorphisms may play a role in Asian SLE patients.[12] Blys-1[13] and previously identified genes responsible for clearance of cell debris such as c1q, C4, and DNAse I also appear to be potential targets for therapy. In a study of 69 SLE patients by Bodano (Spain),[14] decreased levels of DNAse I were reported in the majority of SLE patients in comparison to rheumatoid arthritis or osteoarthritis patients, including 2 SLE patients with mutations that would be expected to lower enzyme activity.

There is little evidence that a breakdown in central (thymic) tolerance plays a key role in human SLE. However, the mechanisms for failure of peripheral tolerance to self-antigens are emerging. The recognition of self-antigen in the presence or absence of costimulatory antigens may be responsible for the mistaken decision to initiate immune responses rather than tolerance. These findings provide the rationale for new treatments with anti-CD20, anti-Blys monoclonal antibody and Blys inhibitors, as well as inhibitors of complement activation. These agents are already in early clinical trials. Another potentially interesting target may be Hmgb1 (high mobility box group 1), which is found in immune complexes from 5 out of 6 SLE patients.[15] Hmgb1 is a secreted proinflammatory mediator and a chromosome-associated protein causing DNA bending. It is released by necrotic cell death, in contrast to products released by apoptotic death that have previously received attention as immune stimulators.

Lipsky (Maryland)[16] reviewed the field of B-cell depletion in SLE. Anolik and colleagues (New York)[17] used rituximab (anti-CD20) in 17 patients. They have previously shown that the level of B-cell depletion at nadir (1-2 months after rituximab 375 mg/m^2) was highly variable (ranging from undetectable to 16% of total lymphocytes.[18] In 11 of 17 patients, B cells were effectively depleted. The residual B cells were CD19-positive with memory phenotype. However, they did not find a significant decrease in anti-double-stranded DNA titers. They concluded that specific B-cell depletion (anti-CD30) in part reverses the abnormalities, but the persistence of autoantibody titers may reflect the presence of long-lived autoreactive plasma cells that are not targeted by this therapy. These results suggest a role of combination therapy to achieve more consistent B-cell depletions. Also, recent studies using anti-CD20 antibody in patients with non-Hodgkin's lymphoma have indicated that patient response partially depends on the Fc gamma receptor, where particular polymorphisms do not allow the monoclonal to bind to natural killer cells efficiently and remove the target CD20-positive cell by antibody-dependent cellular cytotoxicity (ADCC) mechanisms.[19] It will be important to determine whether such FC gamma receptor polymorphisms influence not only CD20 therapy but also the monoclonal antibodies used in therapy of autoimmune disease (ie, infliximab) and constructs that use Fc receptor as part of their structure (ie, etanercept).

Alarcon-Riquelme (Sweden)[20] reviewed the current genetic associations of SLE. The prevalence varies from 0.5% of African American females to .05% of Scandinavian females. This 10-fold difference reflects HLA and non-HLA genes, as well as the "real-world" importance of socioeconomic factors that strongly influence early diagnosis, accessibility to health providers, and outcome due to medication compliance. However, in each group, about 10% of SLE patients have at least 1 relative with SLE or SS. Twin studies continue to show concordance at about 20%, indicating that genetic factors are important and necessary, but not sufficient.

In addition to HLA-DR and associated loci, new studies have indicated an interesting role for locus 2q37 (also known as SLEB2).[21] The candidate gene may be programmed death-1 (PD-1), which is expressed on the surface of T cells and has a ligand on many tissues including antigen-presenting cells, as well as lung, heart, and kidney. There are different alleles of PD-1. PD-1.3A associates with SLE in Norwegian family studies. Based on its structure, PD-1 is predicted to be an enhancer for transcription similar to a family of factors previously called RUNX that influence hematopoiesis and lymphoid development. The concept was proposed that genetic factors could involve important inflammatory genes with a conserved structure but that transcription factors could be polymorphic and thus differentially affect their expression in different tissues to give rise to autoimmune manifestations.

Lupus Nephritis

A multicenter study of MMF vs IVC for induction therapy of severe lupus nephritis was reported by Ginzler (New York).[22] A total of 140 patients from 19 sites were enrolled. Treatment duration was 24 weeks. The MMF dose was started at 1 g/day and escalated to 3 g/day. The IVC dose was based on previous National Institutes of Health (NIH) protocols and both groups received corticosteroids. Both groups showed response with no difference in endpoint creatinine, urine protein, or anti-DNA titers. The proportion of patients in each group with partial (21 on MMF vs 14 on IVC) or complete remission (14 on MMF vs 4 in IVC) was not significantly different. Early withdrawals were 6 in the MMF group and 10 in the IVC group. The study authors concluded that MMF had equivalency to IVC and the patients on MMF had better compliance and fewer serious infections. Due to the importance of this paper, Liang (Massachusetts)[23] presented a critique. He noted that although these studies are extremely promising, caution must still be used in deciding on treatment. First, the follow-up was only 24 weeks. Also, the dose of cyclophosphamide in the NIH protocols was higher than what is generally used in practice and the side effect profile may reflect the use of doses different from those in practice.

Also, in a State-of-the-Art Lecture on the Treatment of Lupus Nephritis, Appel (New York),[24] a member of the study center, gave his current recommendations. For white patients and patients at high risk for toxicity from cyclophosphamide, he uses the Eurolupus protocol, that includes IV cyclophosphamide 500 mg every 2 weeks for 6 doses then either azathioprine or MMF. In these patients, azathioprine or MMF may be started early if the patient seems at higher risk. Azathioprine is significantly less expensive than the MMF. For black patients and those at high risk for progression, he recommends IVC (1-2 g/m^2) plus IV solumedrol monthly for 6 months without MMF, although he may use concurrent MMF if he believes the patient is at especially high risk. However, the longer-term follow-up may allow us to change one of our oldest paradigms in rheumatology, namely the use of high-dose IVC in lupus nephritis induction.

In other therapies of lupus nephritis, the use of a tolerizing agent (LJP 394) was reviewed in 230 patients and overall fewer renal flares (17%) were noted than placebo (20%). Among 189 patients with high-affinity antibody to LJP 394, renal flares on LJP 394 were 8% compared with placebo (22%). This data was presented in the State-of-the-Art lecture and no material was presented in abstract form. However, the degree of enthusiasm expressed by Appel was limited. However, tolerization to autoantigens remains a therapeutic holy grail. Another approach to tolerization may involve manipulation of the plasma dendritic cells. Berkun (Israel)[25] reported that tolerization of plasma dendritic cells can be accomplished in vitro with cells obtained from SLE patients with continuous exposure to self-antigen.

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New Information on Sjögren's Syndrome

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Introduction

At this year's meeting of the American College of Rheumatology, new information on systemic lupus erythematosus and

Sjögren's syndrome was presented in over 400 presentations based on submitted abstracts and in an additional 15 State-of-the-Art presentations dealing with preclinical and clinical features.

Sjögren's

Etiology and Pathogenesis

In Sjögren's syndrome (SS), as in systemic lupus erythematosus, studies on pathogenesis also focused on dendritic cells and interferon alpha. Bave (Sweden)[1] reported that anti-SSA antibodies in combination with apoptotic or necrotic cell material could induce high interferon (IFN)-alfa-production plasmacytoid dendritic cells. The actual IFN-alfa inducer is mostly likely RNA complexed to the RNA-binding proteins. The finding of anti-SS-A antibody is becoming interesting again from a mechanistic point of view. Initially, the SS-A antigen was recognized as important in RNA processing but was largely ignored. Then its emergence on apoptotic blebs resuscitated this molecule as a link to defective cell debris clearance and the adaptive immune system. Now, this complex of protein to tRNAp-like structure may have an additional role as a stimulator of Toll receptors in a manner analogous to double-stranded RNA to initiate or perpetuate the immune response. The tissue localization of immune responses (in salivary and lacrimal glands in SS) provides an interesting challenge to link an antigen found in all nucleated cells to organ-specific immunity. It is proposed that increased cell death in these target tissues (perhaps initiated by a virus) may lead to activation of the innate immune system and subsequent alteration of local chemokines to set up a local microinflammatory environment that subsequently spreads to a more systemic disease.

Triantafyllopoulou (Greece)[2] presented a study of 6 Greek patients with primary SS who had evidence of persistent Coxsackie A4 infection based on the finding of a 94 base-pair gene fragment in 7 of 8 minor salivary gland biopsies and cultured salivary cells from these patients. The positive findings in primary SS patients contrasted with the absence of this 94 base-pair sequence in biopsies from 4 patients with secondary SS and 8 controls. Although these results are intriguing, the number of biopsies remain small and it is unclear whether other ethnic groups will have a similar virus, as previous studies have shown a different HLA association with primary SS in this population than seen in the Western white population.[3] However, it is worth noting that Japanese patients in Kyushi (an area endemic for human T lymphotropic virus type 1) show an increased frequency of this virus in primary SS. Also, patients with hepatitis B[4] and hepatitis C may exhibit features of primary SS.[5,6]

Transforming growth factor (TGF)-beta 1 and tumor necrosis factor (TNF)-alpha polymorphisms were associated with anti-SS B antibody, including a specific allele C at codon 10 of TGF-beta 1 in patients with HLA-DR3.[7] However, the finding of TNF2 polymorphism appeared to result from linkage disequilibrium with the HLA-DR allele. These genetic and autoantibody studies extended previous observations that the genetic predisposition (including HLA-DR and now TGF-1) appears more closely correlated with autoantibody production than with clinical features or outcome. No difference in the polymorphism for estrogen receptor Alpha IVS1 was noted by Whittle (Australia).[8]

As noted above, a key issue remains the preferential localization of the immune response in lacrimal and salivary glands in SS. Barone (Italy)[9] studied the potential role of lymphoid chemokines CXCL13 and CCL21 in salivary gland biopsies from 24 patients.In biopsies with larger foci (score 3 or more) they found a high level of expression of the chemokines, even in the absence of CD21-positive follicular dendritic cells. The lymphocytes had a memory phenotype. In other biopsies with only scattered lymphocytes, the phenotype was memory lymphocytes (CD45R0) in comparison to CD45RA+ lymphocytes in the larger foci. These results indicate the key role of chemokines in helping to organize the focal infiltrates characteristic of SS. From the lymphocyte's perspective on the "homing" to tissues, Shiraishi (Tokyo)[10] studied the ability of CD8+ alphaE beta7- (adhesion molecule) bearing lymphocytes to bind to specific E-cadherins expressed on transfected K562 cells. They found that E-cadherin- (CAD domains 1-5) bound CD8 lymphocytes similar to those found in lacrimal gland biopsies of Japanese SS patients. They proposed that blockage of this adhesion process may be a future strategy for ocular disease. The ability to inhibit "homing" to tissues as a therapeutic strategy has recently been shown effective in both colitis and multiple sclerosis.

Immune Response

During the past several years, there has been increased interest in the potential role of immune responses against the muscarinic receptor on glandular cells that could provide a mechanism to immunologically "denervate" the glands. Previous studies have shown that human SS sera inhibit glandular function when injected into mice.[11] However, it has been difficult to demonstrate autoantibodies that react with the extracellular domain of the human muscarinic M3 receptor. Such a finding would change our overall approach to SS from a T-cell disease to more of a B-cell-mediated

disease similar to myasthenia gravis (characterized by autoantibody to acetylcholine receptor on muscle cells).

In order to further examine the relation of the immune system to the muscarinic M3 receptor in SS, Naito (Japan)[12] found that cultured T cells from SS patients could react with a synthetic peptide derived from the human muscarinic M3 receptor. Although the role in the pathogenesis of B- and T-cell responses against this cholinergic receptor remains an area of active research, it is still too early to tell if this response is a primary or secondary phenomenon. Although immune responses are present against the receptor, the residual glands in SS biopsies continue to express M3 receptor, so the immune mechanisms must act through indirect mechanisms rather than simple destruction of cells bearing the target antigen.

Emamian (Minnesota)[13] studied peripheral blood lymphocytes and used microarray chips to detect the upregulation of about 300 genes in peripheral blood of SS patients when compared with age-matched controls. Many of the identifiable genes that were upregulated had "signatures" associated with upregulated types 1 and 2 interferons. Also, Bombadieri (Italy)[14] found increased levels of interleukin (IL)-18 in sera and in salivary gland biopsies of SS patients, compared with controls and in correlation with characteristic autoantibodies. IL-18 is pivotal in the activation of Th1 cells and would be expected to be coexpressed with IFN-related genes. These results suggest similarity to the more extensive studies performed in systemic lupus erythematosus presented in other sessions of the meeting. However, a study of cytokine transcription of lymphocytes in minor salivary gland biopsies by a different group did not find IFN transcription using polymerase chain reaction methods, although they did detect increased IL-1, TNF, and TGF-beta.[15]

Lavie (France)[16] found increased levels of expression of Blyss (BAFF) on T cells infiltrating the salivary gland biopsies from 14 consecutive SS patients. They used both immunohistology and polymerase chain reaction for detection. Blyss is a newly identified member of the TNF superfamily and plays a role in polyclonal B-cell activation. The expression on T cells was interesting, as the previously reported expression of BAFF has been on macrophages. In a separate study, Gottenberg (France)[17] sequenced the promoter and the 6 exons of the B-stimulator gene Blyss (BAFF) of 6 unrelated SS patients and found several novel single nucleotide polymorphisms (SNPs) at position -871. They then examined an additional 70 SS patients and 90 controls to demonstrate an increased frequency (38%) of this particular SNP. This mutation lies near a putative transcriptional regulatory site for a myeloid-type zinc finger 1 (MZF1) transcription factor. This altered Blyss mRNA was also detected in the monocytes from SS patients, and a higher level of Blyss mRNA was detected than in normal monocytes. This SNP is different from a previously reported polymorphism in Japanese SS patients[18] and may be related to the increased Blyss levels of antigen previously detected in SS patients.

Pan (Germany)[19] detected a frame shift in exon 7 of the SS-A (La) protein in the sera of about 30% of SS patients but not in controls. They proposed that the altered La protein could predispose to apoptosis defects as well as participate in generation of immune responses against La protein. Immunization of mice with the mutant La broke "tolerance" and facilitated epitope spreading to other autoantigens. The mutant mutation was corrected by a second mutation downstream, so that a functional mRNA (but altered) was produced and the mutant product appeared to retard stress-induced apoptosis when transfected into other cells or when transgenic mice expressing this mutation were produced.

Kapsogeorge (Greece)[20] found that cultured salivary gland cells from SS patients expressed a novel form of alternate transcript of B7.2 costimulatory molecule. Although this finding is interesting, it will be important to determine whether this alternate transcription is found in other SS cell lines and other salivary gland cell lines, and whether it is present specifically in biopsies from SS patients.

In studies to identify clinical markers for analysis of disease activity, Gottenberg (France)[21] found increased levels of beta2 microglobulin. These increases correlated with other markers of acute inflammation, including erythrocyte sedimentation rate, C-reactive protein, and total immunoglobulin level. In a separate study, Gottenberg (France)[22] found increased levels of anti-citrulline antibody in about 15% of SS patients. Although this antibody was correlated with a positive rheumatoid factor and synovitis, erosions were not noted on radiographs.

Immune Manipulation

Kok (Maryland)[23] used an adenovirus-associated vector to deliver IL-10 gene into NOD mice via intracannicular injection of the salivary glands or direct inoculation. The transfection resulted in decreased lymphocytic infiltrates when given before the onset of sialadenitis and, to a lesser degree (focus score 2.8 for IL-10 vs 1.9 focus score for vector only), when given after the onset of lymphocytic infiltrates.

Sheyn (North Carolina)[24] performed a meta-analysis on randomized control studies using cholinergic agonists pilocarpine (3 studies) and cevimeline (3 studies). These studies confirmed the ability to increase saliva and measures of oral comfort. They also suggested a positive effect on ocular symptoms even though the US Food and Drug Administration (FDA) approval of these medications did not include ocular symptoms.

Whitcup (California)[25] presented data leading to the FDA's recent approval of topical .05% cyclosporine for keratoconjunctivitis sicca. The pivotal study contained 293 patients in both the active treatment and control groups. In addition to improved tear flow (Schirmer's test without anesthesia), they also demonstrated an improvement in the inflammatory features on conjunctival biopsy. There were fewer lymphocytes and less induction of HLA-DR.

Mariette (France)[26] presented a randomized double-blind study of infliximab (5 mg/kg) in 103 patients for 22 weeks. They did not find significant improvement in the lip biopsies, saliva or flow rate, fatigue score, or joint pain. Seven patients experienced serious adverse reactions (including 6 of 7 in the infliximab group). This double-blind study did not confirm the previous open-label study of 16 patients.[27] Reasons for the difference from the previous study are unclear but are hard to explain on dose (5 mg/kg used rather than the previous 3 mg/kg dose) or entry criteria for study.

In animal models (NZB x NZW mice), immunization with incomplete Freund's adjuvant led to appearance of anti-60 kd Ro antigen.[28] An oral tolerance model in Balb/c mice was reported by Kurien (Oklahoma)[29] in which the mice were fed the 60-kd Ro peptide (residues 287-289), prior to immunization of the peptide in complete Freund's adjuvant. The lymphocytic infiltration into the gland was diminished, as was subsequent epitope spreading from the immunizing peptide to other regions of Ro and La antigens.

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