Asian Journal of Pharmaceutical and Clinical Research
Vol. 4, Issue 1, 2011 ISSN - 0974-2441

Review Article

SJÖGREN'S DISEASE: A COMPREHANSIVE REVIEW ON RECENT CLINICAL AND EXPERIMENTAL FINDINGS IN PATHOGENESIS AND PHARMACOTHERAPY

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ABSTRACT

Sjogren's syndrome is a chronic autoimmune disorder of the exocrine glands with associated lymphocytic infiltrates of the affected glands. Dryness of the mouth and eyes results from involvement of the salivary and lacrimal glands. The accessibility of these glands to biopsy enables study of the molecular biology of a tissue-specific autoimmune process. The exocrinopathy can be encountered alone (primary Sjögren's syndrome) or in the presence of another autoimmune disorder such as rheumatoid arthritis, systemic lupus erythematosus, or progressive systemic sclerosis. A new international consensus for diagnosis requires objective signs and symptoms of dryness including a characteristic appearance of a biopsy sample from a minor salivary gland or autoantibody such as anti-SS-A. Exclusions to the diagnosis include infections with HIV, human T-lymphotropic virus type I, or hepatitis C virus. Therapy includes topical agents to improve moisture and decrease inflammation. Systemic therapy includes steroidal and non-steroidal anti-inflammatory agents, disease-modifying agents, and cytotoxic agents to address the extraglandular manifestations involving skin, lung, heart, kidneys, and nervous system (peripheral and central) and haematological and lymphoproliferative disorders. The most difficult challenge in diagnosis and therapy is patients with symptoms of fibromyalgia (arthralgia, myalgia, fatigue) and oral and ocular dryness in the presence of circulating antinuclear antibodies. The present article reviews the recent developments in pathogenetic factors and pharmacological management.

Key words: Sjogren's syndrome (SS), pharmacotherapy, pathogenesis, autoimmune diseases.

INTRODUCTION

History: Background Review

Dr. Henrik SjÖgren, a Swedish ophthalmologist, is credited with initially describing a triad of symptoms in 1933 that today is commonly known as SjÖgren syndrome (SS). Although SjÖgren is credited with this early description of the syndrome, Mikulicz was probably the first to describe the correlation between lacrimal and salivary gland destruction in his 1892 report of small, round cell infiltrates in the lacrimal and parotid glands. The recognition that SjÖgren syndrome occurs in both primary and secondary forms evolved later in the study of the disease, and SjÖgren syndrome was officially recognized as an autoimmune disorder in the 1960s[1].

SjÖgren syndrome is a chronic autoimmune disorder characterized by patient complaints of xerostomia and xerophthalmia (sicca symptoms) correlated with dysfunction and destruction of the exocrine glands. Xerophthalmia, parotid enlargement, and arthritis are the common symptoms reported. Exocrine gland involvement in SjÖgren syndrome is typified by lymphocytic infiltration of the lacrimal and salivary glands. Although lacrimal and salivary gland dysfunction are the hallmarks of SjÖgren syndrome, involvement of other exocrine glands, such as the upper airway and gastrointestinal mucus-secreting glands, does occur, as do extraglandular manifestations of the disease in as many as one third of patients. SjÖgren syndrome belongs to a family of autoimmune disorders including systemic lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomyositis, and vasculitis and ranks as the second most common rheumatic disease after rheumatoid arthritis[2].

Unlike many autoimmune diseases, SjÖgren syndrome can present in either primary or secondary forms. Primary SjÖgren syndrome is characterized by the sicca complex and often by extraglandular symptoms without any additional connective tissue disorder. In contrast, secondary SjÖgren syndrome occurs in association with another autoimmune disorder, such as rheumatoid arthritis, scleroderma, or lupus. SjÖgren syndrome often has early head and neck manifestations. Because the symptoms of SjÖgren syndrome are often nonspecific, diagnosis and management are often delayed. Otolaryngologists with a high index of suspicion for this disorder may be able to prevent prolonged delays in diagnosis and participate in appropriate diagnostic evaluation or biopsy. Finally, otolaryngologists with an awareness of the systemic manifestations of SjÖgren syndrome may be able to guide other physicians' involvement and therapy. SjÖgren syndrome is recognised as a chronic lymphoproliferative autoimmune disease with disturbances of T lymphocytes, B-lymphocytes, and exocrine glandular cells[3]. Lymphocytic infiltrates are a characteristic histopathological finding in SS. These infiltrates consist of T and B cells. The expression of different cytokines, such as tumor necrosis factor-α (TNF-α) and interferon-α (IFN-α), during the formation and proliferation of these infiltrates has been investigated. There is an overexpression of TNF-α, which is secreted by CD4+ T lymphocytes, mononuclear cells, and epithelial cells[4]. The intraglandular synthesis of TNF-α causes destruction of acini by up-regulation of Fas at the surface of the glandular epithelial cells, stimulation of secretion of type 2 and 9 matrix metalloproteases by epithelial cells, and overexpression of different chemokines[5-7]. IFN-α is produced by activated plasmacytoid dendritic cells in primary SjÖgren syndrome (pSS), and numerous IFN-α-producing cells have been detected in labial salivary glands[8]. IFN-α promotes the autoimmune process by increasing autoantibody production and through the formation of endogenous IFN-á inducers. IFNs have potent immunomodulating properties and are thought to trigger a systemic biological response[9]. Besides the presence of proinflammatory cytokines, recent studies have shown an important role for B cells in the pathogenesis of SjÖgren syndrome. Presence of autoantibodies and hypergammaglobulinemia are both considered to reflect B cell hyperactivity. Systemic complications of SS (SjÖgren syndrome) are associated with this B cell hyperactivity[10]. Moreover, about 5% of SjÖgren syndrome patients develop malignant B cell lymphoma[11]. B cell activating factor (BAFF), also known as B lymphocyte stimulator (BLyS), is an important factor in local and systemic autoimmunity [12].

1.PATHOGENESIS

Although no known chemical or environmental factors are implicated in the pathogenesis of SjÖgren syndrome, it is seen more commonly in patients who have sun sensitivity and in drier climates. Sun sensitivity is related directly to the presence of anti-Ro/SSA antibodies, and sicca symptoms are reported more frequently in drier climates, resulting in higher incidence of diagnosis. Recent studies have elucidated more information in regards to the possible mechanisms that lead to the development of SjÖgren syndrome but also have raised more questions on the exact etiologiy of this disease. Despite multiple theories and associated factors, the exact pathogenesis of this disease is unknown. As commonly noted in autoimmune diseases, multiple infectious etiologies also have been

proposed as triggers of SjÖgren syndrome. Traditionally, Epstein-Barr virus, and more recently, Coxsackie virus, has been implicated in the priming and maintenance of primary SjÖgren syndrome[13]. The causal relationship between viruses and their autoimmune association, however, is unclear. It is likely that decreased clearance within glandular cells secondary to chronic sialadenitis may enable the persistence of viruses rather than the opposite. Antihuman T-cell leukemia virus-1 antibody has been reported in association with primary SjÖgren syndrome in a patient with chronic sensory neuropathy[14]. Additionally, hepatitis C and HIV viruses have been reported in association with a syndrome in affected patients that is very similar to SjÖgren syndrome but lacked the typical autoantibodies associated with the disease. Interestingly, intestinal Tropheryma whippellii-associated sicca complex has been reported also, thus expanding the possibilities of potential causes.[15]

1.1 General

The pathogenesis of SjÖgren syndrome (SS) is multifactorial, and many of the key pathogenic events remain to be elucidated. Although SjÖgren syndrome is well known to have an autoimmune component, recent clinical studies suggest that the disease process involved in SjÖgren syndrome has genetic, immune, and neuroendocrine components. In fact, new theories about the pathogenesis of SjÖgren syndrome suggest that the dryness experienced by patients results from dysfunction of exocrine glandular components as well as from dysfunction in the residual glandular structures. Also, although an autoimmune phenomenon is at the core of pathogenesis in this disease, it is now recognized that the glandular epithelial cells are not innocent targets in this autoimmune attack; rather, defects in glandular development may contribute to the evolution of the autoimmune response [16]. Some of the classical theories are discussed here:

Genetic factors

There is a predominance of HLA-DR genotypes in patients with SjÖgren syndrome, particularly in patients seropositive for antibodies to SS-A and SS-B. In white patients, the extended haplotype seems to be predominantly HLA-DR3. New evidence also suggests that defective glandular development in SjÖgren syndrome may predispose patients to the generation of autoantigens. This aberrant epithelial tissue also plays a secretory role in the disease, because it secretes immune-stimulatory chemokines not seen in patients who do not have SjÖgren syndrome [17].

Immune factors

The evolution of autoimmunity in SjÖgren syndrome remains poorly understood. Clearly, the defective glandular tissue contributes to the development of autoantigens. It seems that numerous immunologic and neuroendocrine factors lead to a milieu in which antigens typically recognized as self become the focus of an immune attack. The glandular tissue with autoreactive antigens then becomes infiltrated with lymphocytes. The dominant infiltrate seems to be CD4 T cells; these lymphocytes subsequently initiate a cascade of events with the release of cytokines including interleukin 1 (IL-1), tumor necrosis factor (TNF), and interferon-gamma. Additional T cells and B cells with autoantibody-secreting capabilities are recruited. This immune response has a destructive effect on the glandular tissue, and the cytokine activity may interfere with the release of acetylcholine and consequent secretory function of the gland [17].

A recently recognized factor important in the perpetuation of this immunologic attack involves the failed apoptosis of these self-reactive T cells. Elucidation of these defects in fas-mediated apoptosis continues to be a focus of research and may also correlate with the premature dysplasia and lymphomatous transformation to which SjÖgren syndrome patients are predisposed[18].

Neuroendocrine factors

Salivary gland biopsies of patients with SjÖgren syndrome suggest that only 50% to 60% of acinar and ductal cells are destroyed because 40% to 50% of the glandular structure remains viable, the symptoms of profound xerostomia and xerophthalmia have puzzled clinicians and scientists for years. Recent clinical studies suggest that dysfunction of the remaining glandular tissue clearly plays a role in SjÖgren syndrome pathogenesis. Proinflammatory cytokines released by epithelial cells and lymphocytes such as TNF and IL-1 seem to impair the neural release of acetylcholine[16]. Further, studies in animal models suggest the presence of M3-muscarinic receptor autoantibodies. Such muscarinic receptor antibodies are purported as contributing to SjÖgren syndrome secretory dysfunction.

2.2 RECENT FINDINGS IN PATHOGENESIS OF SJÖGREN'S DISEASE

2.2.1 T-CELLS

A) Antigen presentation within exocrine tissues

Stimulating progress has recently been made in the elucidation of potential mechanisms for antigen presentation to T-cells within the salivary glands. Close examination of the phenotypes of mononuclear cells infiltrating the labial salivary glands (LSG) of SS patients has revealed that some of these cells, found in conjunction with large CD4+ infiltrations, express the dendritic reticulum cell (DRC) molecule [19]. Electron microscopic study of these cells confirmed that approximately 2% of the infiltrating mononuclear cells were dendritic cells, indicating that active antigen presentation was likely ongoing in these lesions. In addition to these professional antigen-presenting cells, it has been shown that ductal and acinar epithelial cells from SS patients express the co-stimulatory molecules B7.1 and B7.2. [20]

Expression of B7.1 was also observed on epithelial cell lines established from biopsy specimens, and in vitro treatment with IFN--y up-regulated B7.1, B7.2, and HLA-DR on these cells. Expression of this constellation of surface molecules should be sufficient to confer upon these cells the ability to activate T-lymphocytes in an antigen-specific manner, thus increasing the chance for successful presentation of antigen within the salivary glands.

B) **Other adhesion molecules**

In addition to the expression of cell-surface molecules involved in antigen presentation T-cells, other adhesion molecules have also begun to attract attention among SS researchers. Particular interest recently has been focused on the uE137 integrin, which is normally expressed by intra-epithelial lymphocytes in the intestine A study of LSG biopsies from primary and secondary SS patients showed that a small percentage of the mononuclear cells infiltrating the glands express the CXE7 integrin. This follows upon another report showing expression of the same integrin species by T-lymphocytes in synovial tissues of rheumatoid arthritis patients. Interestingly, expression of E-cadherin, a physiological ligand for the aE17 integrin, was also observed[21]. Further study of the roles of various adhesion molecules outside the antigen-presentation process should prove valuable to the understanding of both the origin and the function of mononuclear cell infiltrates in SS, as well as in other autoimmune conditions.

C) **T-cell antigen receptor repertoires**

Previous work on restricted T-cell antigen receptor (TCR) usage among infiltrating T-cells in SS has been expanded to single-cell analysis of CDR3 regions [22]. One-third of the TCR BV2+ cells isolated by cell sorting expressed one of two conserved CDR33 motifs, and three of these six also exhibited some conservation in the CDR33 region. It is somewhat problematic to interpret the relevance of these motifs in the absence of data relating to the antigenic specificity of these clones, but it is of interest that most clones appeared capable of producing both Th1 - and Th2-type cytokines. Another provocative report of conserved TCR sequences in salivary gland-infiltrating T-cells was based in the Aly/Aly mouse model for SS. These mice, which congenitally lack lymph nodes, develop salivary gland infiltrates with age. Among the infiltrating cells in these animals was a subset of NKl.l+ T-cells bearing an invariant a chain. This conserved TCR chain, is the same as that implicated in the pathogenesis of insulin-dependent diabetes, further bolstering the notion that this T-cell subset may be pivotal in the development of autoimmune disease.[23]

D**) Specificities of infiltrating t-cells**

In terms of documented T-cell responses in SS and its models, the newest addition to the spectrum of T-cell auto antigens is the salivary form of c-amylase. Interestingly, "West-Western" screening, using recombinant CDR3 fusion proteins derived from the TCR sequences of infiltrating Tcells of SS patients to screen a salivary gland cDNA library, identified this antigen. This report relied on single-strand conformational polymorphism (SSCP) analysis, rather than actual functional readouts of T-cell activation by ox-amylase, but retains considerable interest in light of the observation that pancreatic ox-amylase produced no apparent expansion of T-cell clones, suggesting a high degree of tissue specificity to this autoreactivity. Among the animal models of SS, the same group has reported T-cell reactivity to ox-fodrin, first observed in the NFS/Sld strain, in the NOD model. The T-cell proliferative response to ox-fodrin arises among NOD splenocytes at 8-10 weeks of age, and is characterized by secretion of IFN--y and IL-2, but little IL-4. This cytokine profile is broadly consistent with the expected inflammatory phenotype and with other reports based on analysis of human SS biopsy materials[24].

2.2.2 ANTIBODIES

The past two years have seen considerable progress not only in terms of defining autoantibody specificities and in terms of responses in SS and its models, but also in delineation of the functional implications of certain autoantibodies. The importance of studying autoantibody specificity and function was highlighted by the demonstration that passive transfer of IgG purified from the sera of SS patients, or from NOD mice with reduced salivary capacity, could affect the stimulated salivary flow rates of healthy recipient mice. This result suggests that autoantibodies, particularly those reactive with exocrine gland muscarinic receptors as discussed below, may play a major pathological role in SS [25].

A) **Autoantibody specificities**

While no single pathogenic autoantibody specificity has yet been demonstrated in SS, several studies have further expanded and defined the spectrum of candidates for such a role. A study comparing patients with SS with controls with oral lichen planus showed that the former group possessed serum IgG antibodies reactive with nuclear and cytoplasmic antigens found in human submandibular gland epithelial cells. Interestingly, cytoplasmic staining was observed when SS IgG was used to probe salivary tissue, but not kidney or pancreas. This indicates that the antigen(s) recognized were tissue-specific, although the identity of these autoantigens remains unresolved. A more specific target of the autoimmune response in SS was identified in a comparison of sera from SS patients, rheumatoid arthritis patients, and normal controls. These researchers found that, like patients with SLE and autoimmune myositis, 30% of SS patients have autoantibodies directed against x- and 3-type proteasome subunits. Thus, this integral part of the antigen-processing machinery is apparently a target of the autoimmune response in SS, with possible implications for processing and presentation of new self-antigens.

In contrast, rheumatoid arthritis patients and controls exhibit no such antibodies. These findings may indicate a crucial linkage between autoantibody responses in SS and the c-antigen-processing machinery that indirectly governs those responses. Other autoantibody specificities with potential functional implications include the anti-a-fodrin response first defined in the NFS/sld mouse model and recently extended to SS patients with and without concurrent lupus. This report showed that antibody to a recombinant ct-fodrin fusion protein was more common in SS patients than in patients with lupus alone, bolstering the potential for use of these autoantibodies as a marker of SS[26].

B) **Clonal relationships among infiltrating b-cells**

There have also been a few notable publications dealing with B-cell activity and antibody production within focal infiltrates in the salivary glands. The identification of anti-Ro and anti-La antibody-secreting B-cells in LSG biopsies of SS patients by the use of biotin-labeled recombinant autoantigens has been demonstrated. The correlations observed in this study between the presence of serum autoantibody and positive staining of LSG specimens with recombinant autoantigens and between the levels of autoantibody in serum and the number of labeled cells in biopsies indicate that this may be a powerful approach in defining the pathogenic potential of novel autoantibodies. Two other studies provide evidence that antigen-driven clonal expansion of B-cells takes place within salivary gland infiltrates in SS. Rearranged Ig genes were amplified by RT-PCR either directly from total LSG mRNA or from DNA from B-cells isolated by microdissection. In both cases, clonally related B-cells were apparent, and there was clear evidence of somatic hypermutation with selection against replacement mutations. These findings strongly indicate that a germinal center- type response is ongoing in the salivary gland infiltrates of SS patients, potentially leading to the selection of high-affinity autoantibodies related to disease progression[27].

2.2.3 CYTOKINES

A) **Overall cytokine profiles in SS**

An inflammatory or Th1 cytokine profile is generally thought to be characteristic of SS. One of the foci of these recent finding has been the production of IFN-y in inflamed salivary tissues in SS and its models. A study of 42 primary SS patients found that mRNAs for Th-1related cytokines, including IL-2, IL-12, IL-18, and TNF-CX in addition to IFN-y, were present in most patients' biopsy samples, while the Th2 cytokine IL-4 was not in evidence. Similarly, Ajjan and co-workers found consistent expression of Thl cytokines in LSG biopsies from SS patients. Both IFN-y and IL-lot were found in the LSG of SS patients, but not in those of the chronic sialadenitis patients in this study. A report presented showing that LSG biopsies from SS patients showed expression of IFN-y, and that this was the principal feature distinguishing them from control tissues. Two other papers present interesting counterpoints to these findings. First, it was found that the frequency of T-cells secreting IL-2 and IFN--y was significantly decreased in the peripheral blood of SS patients as compared with healthy controls. This decrease resembles that reported previously for patients with SLE and polymyositis/dermatomyositis, suggesting a commonality among these rheumatic disorders. Second, a comparison of LSG samples from SS patients and healthy controls showed that both groups consistently exhibited mRNAs for IFN-y and IL-2, but not for IL-4 or IL-5. This strongly indicates that production of Th-type cytokines may be a normal feature of salivary tissue. Clearly, the cytokine profiles present in SS require further study, and care must now be taken to differentiate between cytokines produced by infiltrating cells and those secreted by the salivary epithelium itself[28].

B) **IL-6**

IL-6 has also been a focus of interest in SS for some time, and is known to be elevated in the saliva of SS patients. Increased concentrations of this cytokine have now been demonstrated in the tear fluid of SS patients, with a significant positive correlation between IL-6 levels in tears and LSG biopsy focus scores. Subsequently, it was shown that the level of mRNA coding for IL-6 was increased in the conjunctival epithelium of SS patients. The authors of this second study note that their technique appears to measure cytokine message levels in the epithelium, rather than in any inflammatory mononuclear cells present, and conclude that IL-6 is likely produced by the epithelial cells themselves. While IL-6 is known to have a variety of effects and to act on many cell types, these authors also note that it has been shown to affect the growth and differentiation of epithelial cells. Exactly how these effects may influence the progression of SS is of course a question for further study [29].

C) **Production of cytokines by epithelial cells**

Recent studies emphasize the contributions of various epithelial cells, as well as leukocytes, to the overall cytokine milieu. The elevated concentration of IL-6 in the tear fluid of SS patients appears to reflect the production of this cytokine by conjunctival epithelial cells, rather than by inflammatory cells. A more definitive approach was taken in a study of cytokine production in LSG biopsies from SS

patients. Sections from LSGs were microdissected to isolate infiltrating mononuclear cells, ductal cells, and acinar cells for separate analyses by RT-PCR. The study proves two conclusions; first, it was found that mRNA for many cytokines, including IL-2, IL-4, IL-6, IL-10, TNF-ot, IFN--y, and TGF-13, could be found in all three types of samples. This finding firmly establishes that within the salivary glands, the epithelial cells themselves can influence the overall cytokine profile significantly. Second, the researchers performed separate analyses of cytokine production by ductal and acinar epithelial cells that were adjacent or not adjacent to mononuclear cell foci. In several cases, it was clear that expression of cytokine mRNAs (IL-2, IL-6, IL-10, and TNF-a) differed in the two cases, such that an adjacent lymphoid focus appeared to induce the production of one or more cytokines by the epithelial cells. This strongly suggests that one of the biological consequences of mononuclear cells' infiltration into the exocrine glands in SS is the perturbation of gene expression by the affected epithelium[30].

2.2.4 APOPTOSIS

A) **Factors influencing apoptosis in SS**

Despite the lack of resolution of questions concerning the magnitude of apoptotic activity in SS, significant progress has been made in understanding factors that may influence apoptosis in exocrine tissues. Many of the reports cited above evaluated both apoptotic activity and the presence of apoptosis-related molecules such as Fas, its ligand FasL, and products of the bcl-2 gene family. Thus, it was found by one group that Fas and FasL were both expressed in acinar cells that were surrounded by mononuclear cells, with FasL localized to the apical border. Fas was expressed on the luminal aspect of ductal cells in these patients. Neither Fas nor FasI, was found in control biopsies from subjects without SS. In contrast, two found increased expression of Fas and FasL on acinar and ductal cells of SS patients as compared with controls. All the above three reports agree that the infiltrating mononuclear cells in SS patients' LSG express both Fas and FasL. Apoptosis-related functions of these molecules could, of course, be influenced by the presence of the soluble form of Fas and by IFN-y and by intracellular conditions such as the balance of pro- and anti-apoptotic members of the bcl-2 gene family. Indeed, it has been reported that serum concentrations of soluble Fas are increased in SS patients. Delineation of the expression of the many members of the bcl-2 family and their relationship to apoptosis in the exocrine glands of SS patients is beginning, but considerable effort will be required to sort out the complex interaction among these proteins. Most reports on the subject are in agreement that infiltrating mononuclear cells in SS express Bcl-2. Bcl-2 is generally regarded as an anti-apoptotic protein, apparently as a result of its ability to block release of cytochrome c from mitochondria. Expression of Bcl-2 in infiltrating mononuclear cells is thus consistent with the inhibition of apoptosis in these cells. On the other hand, expression of the pro-apoptotic Bax protein appears to be significantly elevated in LSG biopsies from SS patients, with an increase in the ratio of Bax to Bcl-2. This shift in the balance between pro- and anti-apoptotic regulators could indicate a predisposition in favour of apoptosis in the salivary epithelia of these individuals.

Regulation by soluble factors of apoptosis in salivary epithelia has also been suggested by several recent reports. Transgenic mice expressing IL-10 under control of the salivary amylase promoter exhibit increased TUNEL staining, as noted above. In the same study, stimulation of splenic T-cells with IL-10 was shown to convey the ability to kill primary cultures of mouse salivary gland cells, an effect that could be blocked with antibody to FasL. An increase in apoptotic activity was also observed in NFS/sld mice, which had been rendered estrogen-deficient. Serum antibody to ac-fodrin was also increased in the estrogen-deficient animals as compared with normal controls, and estrogens were found to inhibit Fas-mediated apoptosis of cultured mouse salivary gland cells in vitro. Finally, it was shown that the human submandibular gland cell line HSG expresses increased levels of Fas when cultured with IFN-y. Fas-mediated apoptosis of this cell line is thus enhanced by pre-treatment with IFN-y. If, as some authors suggest, expression of IFN-y in the salivary glands is a principal feature distinguishing SS patients from healthy individuals, this mechanism for promoting cell death may assume pivotal importance in our understanding of SS[31].

3. PHARMACOTHERAPY OF SJOGREN'S DISEASE: RECENT DEVELOPMENTS

Sjögren's syndrome (SS) is a chronic autoimmune disorder. As discussed above it is rheumatic disorder characterized by lymphocytic infiltration and destruction of exocrine glands, mainly of salivary and lacrimal glands, leading to dryness of mouth and eyes. It can occur either alone (primary SS) or in association with almost every systemic autoimmune rheumatic SS). Usually, SS patients have slowly progressive disease confined in exocrine glands; however, in approximately one third of primary SS patients the disorder presents a systemic and progressive course with involvement of diverse extra glandular sites and in a small but significant number of patients with lymphoid neoplasia development. Although the aetiology of SS remains unknown, chronic immune system stimulation is thought to play a central role in the pathogenesis of the disorder, as illustrated by several indices of immunological hyperactivity, including various autoantibodies, polyclonal hypergammaglobulinemia and circulating paraproteins. To date, treatment of SS remains largely empirical and symptomatic, and no clinical trial has been proved capable to change the course of the disease.

3.1 Pharmacotherapy: Approaches towards Pharmacological Management of SS

Although SjÖgren syndrome is unlikely to be primarily managed by the OMS, a thorough knowledge of the tenants of treatment is important. Xerostomia is the hallmark of the disease process and the most likely component to be encountered and treated by the OMS. Certainly, impeccable oral hygiene is vital because of the diminished anticariogenic properties of salivary flow, and the avoidance of refined carbohydrates. Ideal treatment should address xerostomia, prevention of oral complications, stimulation of salivary flow, and repair of inflamed salivary glands. Currently, there is no panacea for patients who have SjÖgren syndrome. Adequate hydration remains the simplest yet most effective means to treat xerostomia. Frequent small sips of water not only rehydrate the oral cavity but also cleanse and reduce microbial load. Avoidance of dehydration is paramount to maintain baseline salivary flow. Caffeinated sodas should be avoided because of the diuretic effect of caffeine and the acidity of the soda. Fluoride carriers and remineralization solutions may be necessary for caries control. The use of nighttime humidifiers is a consideration that will minimize oral drying during sleep, as this is the diurnal nadir of salivary flow. Several modes of salivary stimulation are available.

Ranging from topical to systemic, these therapies are based upon some remaining secretory capacity of the salivary glands. The disadvantage of all these therapies is their transient nature, although symptomatic relief may persist beyond the period of increased salivation and is likely related to the obtundant effects of saliva on the oral mucosa.[32] Local therapies include sugar-free gums, candies, or lozenges as stimulants to gustatory and masticatory salivary flow. Xylitol is an acceptable artificial sweetener and has been shown to reduce caries. Clinical trials have supported the use of anhydrous crystalline maltose lozenges as an effective means to treat xerostomia.[33] Oral Pilocarpine 5 mg three to four times daily also has been recommended. The use of this parasympathomimetic has been around for over 100 years and has been shown in several clinical trials to be an effective means to stimulate salivary flow. There is no tolerance associated, and adverse reactions including sweating, flushing, and frequent urination are rare.

This drug, however, is contraindicated in acute narrow-angle glaucoma, uncontrolled asthma, and acute iritis. Other effective agents include Cevimeline, which may have a longer duration of action than Pilocarpine, but similar pharmacologic profile, Bromhexine Interferon-alpha in indictable or lozenge form, which has shown increased salivation and decreased salivary gland inflammation, Infliximab, a tumour necrosis factor a blocker-2.

Interestingly, favourable early results have been seen with tibolone, a synthetic steroid with androgenic properties, when used to treat patients who have SjÖgren syndrome. Tibolone, when given orally at a dosage of 2.5 mg/d, has been shown to increase oral, ocular, and vaginal lubrication in postmenopausal women[34]. Xerophthalmia is also a key target of anti- SjÖgren syndrome therapy and often is addressed by the ophthalmologist. Local therapy includes mainly nonpreservative-containing artificial tears in the form of eye drops, gels, or ointments. Some, in addition to warm ocular compresses and massage aimed at reducing meibomian inflammation, advocate topical steroids. Temporary or permanent punctal occlusion may benefit those who have severe ocular symptoms. In addition, systemic administration of androgens methyl-testosterone or mesterolone and cyclosporine has been linked with beneficial effects on lacrimal and meibomian function. Some authors even have suggested transplantation of minor sublingual salivary glands.[35] For the 6% to 10% of patients who may progress into lymphoma, a complete workup to assess other locations and staging is recommended. Any parotid focus of lymphoma is typically treatable with radiotherapy and any change in size, colour, or architecture of the involved parotid gland andates repeat biopsy.

Non-visceral manifestations such as arthralgia and myalgia are generally treated with salicylates, nonsteroidal agents, and hydroxychloroquine. As in systemic lupus erythematosus, corticosteroids are effective but limited by their usual side-effects including osteoporosis, diabetes, cardiovascular effects, and mood disruption. Patients with Sjögren's syndrome have greater problems with corticosteroids, including acceleration of periodontal disease and oral candidosis. Another difficulty is low tolerance of NSAIDs resulting from dysphagia secondary to decreased salivary flow and oesophageal motility, as well as the increased frequency of gastro-oesophageal reflux disease[36,37]. For treatment of arthralgias, generic NSAIDS can be prepared as a topical cream or as a rectal suppository for patients with difficulty swallowing tablets. Among the slow-acting drugs, hydroxychloroquine is useful in decreasing arthralgia, myalgia, and lymphadenopathy as in some patients with systemic lupus erythematosus.[38] Hydroxychloroquine (6–8 mg/kg daily) was used in patients with Sjögren's syndrome who have raised ESR and polyclonal hyperglobulinaemia to lower frequency of flares of arthralgia, rash, and lymphadenopathy. Kruize and colleagues[39] also found that hydroxychloroquine improved ESR but did not increase tear flow volumes. For visceral involvement, including vasculitic skin lesions, pneumonitis, neuropathy, and nephritis, corticosteroids are used in similar doses to those used in systemic lupus erythematosus. Drugs such as hydroxychloroquine, azathioprine, and methotrexate are used to help taper the corticosteroids.[40] Methotrexate seems to be more useful than azathioprine in Sjögren's syndrome.[41,42] Leflunomide is likely to prove useful in selected patients with Sjögren's syndrome,[43] as in systemic lupus erythematosus. In some patients with Sjögren's syndrome, cyclosporine can be used[44]. However, the tendency to interstitial nephritis limits the usefulness of the drug. Owing to side-effects, the use of mycophenolate mofetil is being explored as an alternative to cyclophosphamide in treatment of vasculitis[45].

One pilot study suggested that an inhibitor of tumour necrosis factor (infliximab) might be beneficial,46 but subsequent multicentre trials did not confirm the results.[47] Similarly, double-blind studies have not shown significant benefit with etanercept.[48,49] As in other autoimmune disorders, there is increasing interest in B-cell depletion through the use of monoclonal antibody to CD20 (rituximab).[50] Outcome measures in Sjögren's syndrome are important and have been the subject of recent conferences,[51] with assessment subdivided into: exocrine (including sicca symptoms and signs) and nonexocrine disease activity and systemic symptoms (objective evidence of extraglandular activity and damage (present for over 6 months); health-related and generic quality of life (including fatigue); standard approaches to adverse events and toxic effects; and health-economic elements. The use of biomarkers similar to those in systemic lupus erythematosus[52], including autoantibodies, chemokines, and cytokines can supplement clinical measurements.

3.2 RECENT DEVELOPMENTS IN PHARMACOLOGICAL TREATMENT OF SJÖGREN'S SYNDROME

Cristina[53] ***et al*** studied on cytokine inhibition and found that it is one of the most attractive approaches to treat autoimmune diseases. Attempts to block the effects of cytokines with oral small molecules have not been successful in the clinic to date, but preliminary results obtained with JAK inhibitors are very encouraging and point at the JAK family as one of the most attractive targets so far. Preventing tissue damage remains an unmet medical need that could be achieved by inhibiting the migration of inflammatory cells, ideally at the early stage of the disease. Targeting Th17 cells appears to be a promising approach to prevent aggressive neutrophil and macrophage tissue infiltration. This field is novel and in the near future will provide a better understanding of the function of these cells and an avenue for drug development. The ultimate goal to treat autoimmunity is to develop efficacious therapies that will lead to a sustained remission of the disease. This approach needs to include a strategy directed at restoring immunological self-tolerance while preserving the immune response against invading pathogens. The discovery of the microRNAs that control the genetic programs of regulatory and effector lymphocytes are an exciting field that will increase our understanding of the immune system in the near future. It is clear that the limited number of successful therapies to treat these diseases underscores the need for a better understanding of the mechanisms and players involved in autoimmunity and tolerance. However, with the continued interest in developing additional novel biologics and small molecule inhibitors there are additional hope on the horizon for patients with autoimmune disorders.

Jing [54] ***et al*** studied the mucosal administration of α-fodrin effectively suppresses the production of SS-related antibodies, prevents the in vivo production of inflammatory cytokines, such as IFNγ, and increases the number of Foxp3+ CD4+CD25+ regulatory T cells. This study raised the hypothesis that mucosal administration of α-fodrin possibly inhibits the progression of experimental SS autoimmunity.

Ikuko[55] ***et al*** studied the effect of CD20 monoclonal antibody treatment on the disease in Id3 knockout mice. Antibody treatment at 2-month intervals led to efficient and sustained B-cell depletion in Id3 knockout mice. A significant improvement of histopathology was observed accompanied by the recovery of saliva secretory function after CD20 antibody treatment. They further showed that serum immunoglobulin G3, which is abnormally high in untreated Id3 knockout mice, was reduced after CD20 antibody treatment. This study establishes a new animal model for immunotherapy of Sjögren's symptoms and suggests a possible link between immunoglobulin G3 and disease pathology in Id3 knockout mice.

Takagi[56] ***et al*** worked on, cevimeline hydrochloride hydrate clinically and applied it to the patients with Sjögren's syndrome for the treatment of xerostomia. Oral doses of cevimeline significantly improved subjective symptoms of dry mouth and dry eyes, and increased salivary flow. Given the satisfactory efficacy and safety of the cevimelinegargle in healthy subjects, we next tested whether the same treatment was effective in patients with Sjogren's syndrome.

Voulgarelis[57] ***et al*** evaluated the efficacy of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) in combination with rituxan in SS patients with diffuse large B cell lymphomas (DLBCL), and o determine the outcome in such patients. They concluded that the addition of Rituxan to standard CHOP chemotherapy results in improved treatment outcome in SS patients with aggressive DLBCL, without increasing toxicity.

Serge[58] ***et al*** This initial experience in patients with active pSS demonstrated that four doses of 360 mg/m2 epratuzumab immunotherapy appears to be safe and well-tolerated when infused within 45 minutes, with clinically significant responses observed in approximately half the patients for at least 18 weeks in the presence

of modestly decreased (39%–54%) circulating B-cell levels, and with evidence of minimal immunogenicity, as measured by HAHA. We conclude that eprattuzumab may be a promising therapy in patients with active pSS and that a multicentre, randomised, double-blinded, controlled study to confirm the beneficial effects of anti-CD22 therapy is indicated.

Yue Wang[59] ***et al*** reported the evidence that it has accumulated suggesting that a Th1/Th2 cytokine imbalance has a role in the pathogenesis of SS. Currently, only palliative treatment is available. Ophiopogon japonicus, a common Chinese herbal, has been used to treat sicca-associated disorders in traditional Chinese medicine for centuries. Thus, this study provided a basis for the use of Ophiopogon japonicus in SS.

S Yamada[60] ***et al*** studied the treatment response to interferon alfa (IFN-α) is described in three consecutive cases of two forms of Sjogren's syndrome associated neuropathy (SSN)—two with sensory ataxic ganglionopathy and one with sensorimotor neuropathy with demyelinating features. All responded well to IFN-α in terms of neuropathic symptoms, sicca symptoms, antibody titres, and findings in salivary gland biopsy specimens. IFNa thus showed promise in treating both SSN and the underlying Sjo¨gren's syndrome.

Nishiyama[61] ***et al*** studied the apoptosis in K-13182-treated mice, the decrease in tear secretion was also prevented compared to the control mice. In addition, the apoptosis and the expression of FasL (CD178), perforin, and granzyme-A was suppressed in the lacrimal glands of K-13182-treated mice. Therefore, K-13182 demonstrated the possibility of therapeutic efficacy for the inflammatory region of autoimmune disease model mice. These data reveal that VCAM-1 is a promising target molecule for the treatment of autoimmune diseases as a therapeutic strategy and that K-13182 has the potential as a new anti-inflammatory drug for SS.

Margaret[62] ***et al*** determined the effects of lymphotoxin-beta receptor (LTβR) pathway blockade on Sjögren syndrome (SS) - like salivary gland disease in non-obese diabetic (NOD) mice. Our findings show that blocking the LTβR pathway results in ablation of the lymphoid organization in the NOD salivary glands and thus an improvement in salivary gland function. This study shows that blocking the LTβR pathway in NOD mice ablates lymphoid neogenesis in the salivary glands and this is accompanied by an improvement in salivary gland function. The effect of interfering with the LTβR axis has not previously been explored in SS-like disease.

Peter[63] ***et al*** studied the Mycophenolate sodium treatment in patients with primary SjÖgren syndrome. Their findings of this open-label pilot trial in patients with pSS suggest that MPS might improve subjective glandular and extraglandular manifestations as well as some laboratory parameters. MPS promises to be an additional therapeutic option in patients with pSS, particularly in those with early disease. Controlled studies including larger numbers of patients with shorter disease durations are necessary to assess more comprehensively the efficacy and safety of MPS in pSS.

Schot[64] ***et al*** studied the effect of nandrolone decanoate on Sjogren's syndrome like disorders in NZB/NZW mice This study further documents the effects of ND in B/W mice. The results clearly indicate that 3 weekly injections (started at 4 weeks of age for 9 months) reduce the formation and growth of mononuclear infiltrations in the submandibular gland and prevent thereby destruction of glandular tissue.

Odile[65] ***et al*** In an attempt to analyze the regulated gene expression in lymphocytes by an HIV-suppressive immunomodulator, we have identified and cloned a novel gene encoding a 56-kDa protein, named SS-56, which is structurally related to the 52-kDa Ro/SSA antigen. In conclusion, they have cloned the full-length cDNA of a novel autoantigens SS-56 that seems to share, besides sequence homology, molecular and physiological characteristics with SSA-52. Autoantibodies's against SS-56 were detectable in sera of patients with SS or with SLE. Importantly, some patients who showed no reactivity against the classic SSA and SSB antigens were found to present detectable autoAb's to SS-56. Taken together, these findings define a new cellular target of autoimmune responses and point to the potential application of this protein in the diagnosis of SS and SLE. The biologic implications of these results in the pathogenesis of autoimmunity await further studies and a comprehensive profiling of autoAb responses to SS-56 in other autoimmune connective tissue diseases.

Aragona[66] ***et al*** evaluated the effect of oral Pilocarpine treatment on conjunctival epithelium of patients with Sjögren's syndrome (SS). Moreover, the results showed that the conjunctival imprinting showed an increase of goblet cells number at T1. At T3, the number of goblet cells significantly decreased. An improvement of dry mouth started at T1 and returned towards baseline values at T3. For ocular symptoms, burning and foreign body sensation was improved at T1 while ocular dryness improved at T2. But showed a statistically significant improvement at T2. In conclusions, Oral Pilocarpine induced an increase in goblet cells number and an amelioration of conjunctival epithelium not dependent on tear secretion.

Moutsopoulos[67] ***et al*** studied the immunological consequences of systemic thalidomide treatment in patients with SS. They measured cytokine (tumour necrosis factor a (TNFa), interleukin (IL) 6) and soluble receptor (sIL2R) levels in patient and control plasma, before and after thalidomide treatment. Peripheral blood mononuclear cells were examined by FACS analysis for potential changes in specific cell populations (T cells, B cells, monocytes), and for the expression of activation markers (CD25, HLA-DR), costimulatory molecules (CD40, CD40L), TNF receptors, chemokine receptors, and adhesion molecules (L-selectin (Lsel)). The results show that none the less, statistically significant changes in markers of cell activation were recorded in the four treated patients. Before treatment, HLA-DR, TNFRI, CXCRI, and CXCRII were raised in the patients compared with healthy controls and their expression was down regulated after treatment. B cell numbers and expression of the adhesion molecule L-sel also declined with thalidomide. Conclusion: Significant changes in measures of cell activation were detected during thalidomide treatment within this limited study, which upon further investigation may offer insight into the underlying immunoregulatory pathways of thalidomide.

CONCLUSION

SjÖgren syndrome (SS) is complex inflammatory autoimmune disease, and its treatment is often difficult and less than optimal Because most of the current therapy for SjÖgren syndrome is mostly symptomatic, there remains a dearth of treatment directed at the exact etiology behind the disease. Future therapy likely will be directed at more tissue-specific receptors, resulting in less side effects. The ultimate goal to treat autoimmunity is to develop efficacious therapies that will lead to a sustained remission of the disease. This approach needs to include a strategy directed at restoring immunological self-tolerance while preserving the immune response against invading pathogens. In conclusion, treatment of patients with autoimmune diseases may be improved by using new therapeutic approaches that interfere with the humoral response rather than depleting B cells, or combining the different approaches, may perhaps result in improvements in clinical outcomes. With the continued interest in developing additional novel biologics and small molecule inhibitors there is additional hope on the horizon for patients with autoimmune disorders.

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