SJÖGREN'S SYNDROME: RECENT ADVANCES IN PATHOGENESIS AND PHARMACOTHERAPY

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Summary

Sjögren's syndrome is a chronic autoimmune disorder of the exocrine glands with associated lymphocytic infiltrates of the affected glands. The molecular biology of these tissue-specific autoimmune processes can be studied through biopsy since these glands are easily accessible to it. 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. 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 of Sjogren's syndrome.

Keywords: Sjögren's syndrome, Pharmacotherapy, Pathogenesis, Autoimmune disease.

Introduction

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[1]. Primary SjÖgren syndrome is characterized by the sicca complex and often by extra glandular 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. An Otolaryngologist 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.

Sjögren's syndrome: A background review

In 1933, a Swedish ophthalmologist, Dr. Henrik SjÖgren, is credited with initially describing a triad of symptoms that today is commonly known as SjÖgren syndrome. 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[2].

Pathogenesis:

Sjögren's 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. 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 over expression 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[5,6,7]. IFN-α is produced by activated plasmacytoid dendritic cells in primary Sjögren's 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's syndrome. Systemic complications of Sjögren's syndrome are associated with this B cell hyperactivity[10]. Moreover, about 5% of Sjögren's 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]. 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. 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].

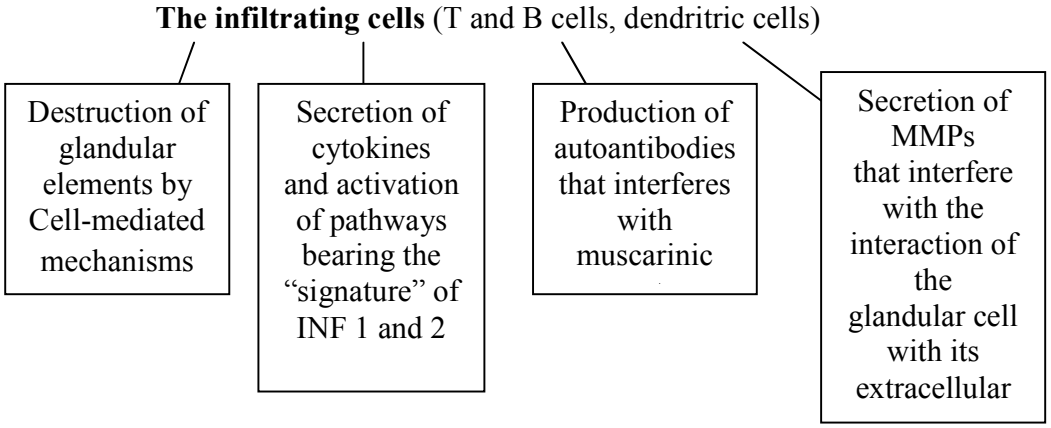

Fig.1. Main mechanisms of gland-induced dysfunction in pSS. INF, interferon; MMP, metalloproteinase.

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] 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]

CLASSICAL THEORIES:

a) Genetic factors: There is a predominance of HLA-DR genotypes in patients with SjÖgren syndrome, particularly in patients seropositive for antibodies to SS-A (SjÖgren syndrome-A) and SS-B (SjÖgren syndrome-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].

b) Immune factors: It seems that numerousimmunologic 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. 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].

c) 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.

SJÖGREN'S SYNDROME: RECENT FINDINGS IN PATHOGENESIS OF DISEASE.

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 SjÖgren syndrome patients has revealed that some of these cells, found in conjunction with large CD4+ infiltrations, express the dendritic reticulum cell (DRC) molecule [19]. 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]

b) Specificities of infiltrating t-cells:

In terms of documented T-cell responses in SS (SjÖgren syndrome) and its models, the newest addition to the spectrum of T-cell auto antigens is the salivary form of c-amylase. Interestingly, this antigen was identified by "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. 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 SjÖgren syndrome, T-cell reactivity to ox-fodrin, first observed in the NFS/Sld strain, has been reported in the NOD model by the same group. 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. [21]

2. Antibodies:

While no single pathogenic autoantibody specificity has yet been demonstrated in SjÖgren syndrome, several studies have further expanded and defined the spectrum of candidates for such a role. A study comparing patients with SjÖgren syndrome 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 SjÖgren syndrome 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. 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 SjÖgren syndrome patients with and without concurrent lupus. This report showed that antibody to a recombinant ct-fodrin fusion protein was more common in SjÖgren syndrome patients than in patients with lupus alone, bolstering the potential for use of these auto antibodies as a marker of SS[22].

3. Cytokines profiles in SjÖgren syndrome:

A study of 42 primary SS (SjÖgren syndrome) patients found that mRNAs for Th ,-related 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 SjÖgren syndrome patients, but not in those of the chronic sialadenitis patients in this study. 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 SjÖgren syndrome 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 SjÖgren syndrome 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[23].

4. Apoptosis:

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.

Indeed, it has been reported that serum concentrations of soluble Fas are increased in SS patients. 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 SjÖgren syndrome patients from healthy individuals, this mechanism for promoting cell death may assume pivotal importance in our understanding of SjÖgren syndrome.[24]

PHARMACOLOGICAL TREATMENT: RECENT DEVELOPMENTS

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. 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.

a). **Cristina *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[25].

b). **Jing *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 Sjögren's syndrome autoimmunity[26].

c). **Ikuko *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[27].

d). **Takagi *et al*** .worked on, cevimeline hydrochloride hydrate clinically and applied it to the patients with Sjo¨gren'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[28].

e).**Voulgarelis *et al.*** evaluated the efficacy of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) in combination with rituxan in Sjögren's syndrome 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 Sjögren's syndrome patients with aggressive DLBCL, without increasing toxicity[29].

f). **Serge *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 epratuzumab may be a promising therapy in patients with active pSS (primery Sjogren's syndrome) and that a multicentre, randomised, double-blinded, controlled study to confirm the beneficial effects of anti-CD22 therapy is indicated[30].

g). **Yue Wang *et al*** .reported the evidence that it has accumulated suggesting that a Th1/Th2 cytokine imbalance has a role in the pathogenesis of Sjogren's syndrome. 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[31].

h). **S Yamada *et al*** .studied the treatment response to interferon alfa (IFN-α) is described in three consecutive cases of two forms of Sjo¨gren'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 Sjogren's syndrome associated neuropathy and the underlying Sjögren's syndrome[32].

i). **Nishiyama *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 Sjögren's syndrome [33].

Conclusions

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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