Recent developments in the diagnosis and management of Sjögren's syndrome

Sjögren's syndrome (SS) is a common immune disease that mainly affects the exocrine glands, which clinically present xerostomia, keratoconjuctivitis sicca and serological autoantibodies including rheumatoid factor, antinuclear antibody, anti-SS-A and anti-SS-B. The prevalence of SS is high but underestimated in the general population. SS may involve many other organs and tissues including lung (interstitial lung disease), kidney (renal tubular acidosis and hypokalemia), nerve (peripheral neuropathy), vessel (vasculitis, Raynauld's phenomenon), bladder (interstitial cystitis), lymph node (lymphaenopathy), liver (autoimmune hepatitis), pancreas (pancreatitis) and GI (reflux esophagitis, peptic ulcer). In 2010, a new disease activity, the European League Against Rheumatism (EULAR) Sjögren Syndrome Disease Activity Index (ESSDAI) was proposed. Diagnosis of SS is based upon the 2002 classification criteria of SS, which originated from the 1996 European classification criteria. Methods for diagnosis of SS include salivary flow assessment, salivary gland scintigraphy, Schimer's test, Rose Bengal test and minor salivary gland biopsy. Treatment of dry mouth and dry eye requires muscarinic agonists, for which two drugs are now available; pilocarpine and cevimeline. Hydroxychloroquine is not useful for sicca syndrome, however, it may be effective to relieve arthralgia. Active immunotherapy is considered when the patient has pulmonary, neurologic and renal involvement. Corticosteroid, cyclophosphamide, azathioprine, mycophenolate mofetal (cellcept), mizoribine and cyclosporine are the immunosuppressive drugs that have been used for SS with systemic manifestations. TNF-α blocker has been used in SS but, in general, it demonstrated no benefit to relieve oral or eye dryness. More recently, rituximab, a B cell directed therapy, was reported to have efficacy for sicca symptoms or pulmonary, neurologic involvement. In this article, we demonstrate current diagnosis and therapy for SS.

KEYWORDS: autoantibody ▪ diagnosis ▪ muscarinic agonists ▪ Sjögren's syndrome ▪ treatment

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Epidemiology

Sjögren's syndrome (SS) is a common systemic autoimmune disease and in the USA, it affects 2–4 million people [1–4]. Primary SS occurs in 0.2–1.4% of the female population [5,6]. In the Chinese population, the prevalence rate was 0.33–0.77% [7]. In our rheumatology clinical practice, at least 5% of outpatient clinic patients were diagnosed with either primary or secondary SS.

Glandular manifestations

The most common symptoms of SS are dry eye and dry mouth [8–10]. Symptoms of dry eye may cause itching, sandy sensation, burning and pain. It may develop first before the oral dryness. Patients usually visit the ophthalmologist and then refer to rheumatologist. During eye examination, conjunctivitis is the most common presentation and occasionally, corneal ulcers or perforation and visual impairment may occur.

With regards to oral dryness, initially patients complain that they need to drink water frequently in order to relieve their dry mouth. Later, oral complications after long duration of diminished salivary secretion may encounter. Frequent oral ulcers, fissuring of tongue, candidiasis, periodontitis, dental caries and loss of teeth are major problems that closely associate with the unrelieved oral dryness. Besides dry eye and mouth, patients also may complain of dry skin or vagina.

Extraglandular manifestations

Sjögren's syndrome, is a systemic disease, which may involve different organs and cause arthritis or arthralgia, Hashimoto's thyroiditis, lymphodenopathy, B-cell lymphoma, interstitial pulmonary or lymphocytic alveolitis, vasculitis, neuropathy, Raynauld's phenomenon, renal involvement, chronic atrophic gastritis, reflux esophagitis or peptic ulcer, pancreatitis, primary biliary cirrhosis and autoimmune hepatitis [8–15]. When the disease duration is longer than 10 years, a higher prevalence of parotid gland enlargement, lung involvement, and peripheral neuropathy is seen more frequently.

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Pulmonary manifestations

Lung involvement is not uncommon in patients with SS [15–18]. Routine survey, including chest x-ray, pulmonary function test and high resolution computed tomography, can demonstrate some abnormal chest findings even in patients without chest symptoms. The reported frequency of pulmonary involvement ranged from 9 to 75%. The main pathologic findings in the lung consist of interstitial lung disease (ILD) and small airway abnormalities.

Clinical features in SS are variable in each patient. A persistent cough with or without sputum may last for a long period. Symptoms may get worse if an infection, including the common influenza, is superimposed. Exertion dyspnea is observed when the patient has increased lung damage or diffuse pulmonary fibrosis.

For early and small lesions, chest x-ray may not be sensitive to visualize. By contrast, high resolution computer tomography (HRCT) provides a good image to detect either ILD or small airway lesions. The most common ILD are nonspecific interstitial pneumonitis (NSIP) and lymphocytic interstitial pneumonitis. Japanese investigators classified HRCT findings of primary SS lung involvement into five patterns: interstitial pneumonia; lymphoproliferative disorder; bronchiolitis; cryptogenic organizing pneumonia; and unclassified [18]. Another investigator divided the lung disease in SS into: usual interstitial pneumonia (UIP)-like, NSIP-like, lymphocytic interstitial pneumonitis-like and bronchiolitis-like [15]. One recent study from China by Shi *et al.* demonstrated in seven patients with dyspnea and cough and the lung specimens after transbronchial biopsy demonstrated NSIP in five patients with either follicular bronchiolitis or organizing pneumonia, and only bronchiolitis in two patients [16].

Treatment is mainly corticosteroids. Other immunosuppressive agents have been used including cyclophosphomide, azathioprin, mycophenolate moftel, leflunomide, and more recently, rituximab [19–21]. Owing to the lack of large, randomized clinical trial, the standard and classical therapy in SS with pulmonary involvement has not yet concluded at the moment. The early intervention of active immune therapy is indicated when the patient has progressive chest symptoms or prominent abnormal chest or HRCT findings.

Bladder abnormality in SS

Among the immune diseases, the leading cause of interstitial cystitis (IC) is SS. The most frequent manifestations of cystitis are frequency, urgency, nocturia and suprapubic pain [4,22]. After urodynamic and cystoscopic examination, the bladder abnormality may be due to detrusor overactivity (DO), bladder hypersensitivity or IC [23,24]. Wang *et al.* proposed DO was antibody-mediated cholinergic hyperresponsiveness [23]. In the human body, the muscarinc receptor, M3R, is a prominent receptor on the detrusor muscle. However, the abnormal discharge from different nerve or autoantibody binding to M3R may initiate the excessive cholinergic contraction of the urinary bladder.

Defects in the glycocalyx, including the alteration of bladder epithelial glycoconjugates, has also been recognized to be the risk factor for IC. Early study showed both galectin-3 and galectin-4 were expressed in rabbit bladder [25]. Further animal studies by Buckley *et al.* found glycoproteins rather than glucosaminoglycans, were the major components of the bladder epithelium and that the former included a mucin [26]. However, observation of the bladder wall by electron microscope did not show the differences in the morphologic appearances of the glycocalyx of urothelial cells in patients with IC when compared with controls.

Muscarinic receptor antagonist therapy was reported to give a good response for DO. However, such therapy may precipitate the oral dryness and some patients may not be able to tolerate it. Other therapy using some neurotoxins, including botulinum toxin, have been tried but efficacy should be determined by the future large clinical study [27].

Renal involvement

In a large survey of 7276 patients at the Mayo Clinic (MN, USA; carried out between 1967–2007), 24 patients had renal involvement and received renal biopsy. A total of 17 out of 24 patients had tubulointerstitial nephritis (TIN) with chronic TIN (11/17, 65%) [12].The presentation of renal tubular dysfunction includes type 1 renal tubular acidosis, renal calculi and hypokalemia. Cryoglobulinemia and proteinuria are seen occasionally. Screening for renal involvement in primary SS should include urine examination, serum creatinine and serum potassium.

Steroids, cyclophosphamide or rituximab are considered to treat SS patients with renal involvement. For renal tubular acidosis and lower serum potassium, we may add sodium bicarbonate or potassium citrate. Hyperchloremic acidosis is corrected and the occurrence of calculi reduced by the use of usually 5–10 g sodium bicarbonate per day divided to 3–4 doses. Sodium citrate

can also be used (Shohl's solution: 70–140 ml divided into 3–4 doses). Thiazide diuretics are sometimes used in nepholithiasis and urolithiasis in order to diminish the secretion of calcium to urine. Large, randomized clinical trials are needed to determine the efficacy of those immunosuppressive drugs.

■ Neurologic involvement

Neurologic manifestations are not uncommon in SS but often unnoticed if neuropathy is subclinical or mild. The prevalence of neurologic manifestations in SS varied between 10 and 60% [1,4,10]. In general, CNS involvement is seldom seen. Symptoms may include convulsion or focal epilepsy when the brain is involved. Cranial nerve palsy or spinal cord myelopathy may also be involved [9,28].

By contrast, peripheral neuropathy is the common clinical presentation in SS patients. There are different subtypes of peripheral neuropathy including sensory ataxia neuropathy, mononeuropathy, polyneuropathy, polyradiculopahy and autonomic neuropathy [10,29–31]. The sensory neuropathy (small fiber neuropathy) is one of the common manifestations in peripheral neuropathy [31]. During an attack, patients suffer from severe pain over the face or extremities and so on. Different treatment strategies will be applied based upon the pathogenetic mechanisms. Sensor axial neuropathy is caused by ganglionitis and steroids are ineffective, therefore intravenous immunoglobulin (IVIG) or plasmaphoresis is instead considered. Steroids are effective in SS with mononeuropathy (mononeuritis multiplex), which the mechanism is vasculitis mediated.

■ Lymphoma in SS

From 1981 to 2008, Baimpa et al. in Greece analyzed 536 patients with primary SS and eventually, 40 cases were confirmed to have malignant lymphoma (7.5%) [14]. The risk factors to develop lymphoma include neutropenia, cryoglobulinemia, splenomegaly, lymphoadenopathy and low complement 4 (C4) levels.

■ Gastrointestinal involvement

One study from China revealed 32.8% of 573 primary SS patients had liver abnormality, including elevation of liver enzymes or total bilirubin [8]. After evaluation of pancreas by ultrasound, 5.6% of primary SS patients were identified with pancreatic lesions and among them, eight cases had acute pancreatitis and 16 cases had chronic pancreatitis. The results are similar to the study from Japan that autoimmune pancreatitis is not uncommon in primary SS with incidence ranging from 1.86 to 6.6% [13,32]. As a matter of fact, the autoimmune pancreatitis might be IgG4-related sclerosing pancreatitis [33,34]. Besides, higher concentrations of IgG4 have been reported in patients with Mikulicz's disease [35].

One recent study evaluated the liver disease in 202 patients with primary SS and only 1.7% had autoimmune hepatitis and 1% had primary biliary cirrhosis [36]. However, the prevalence of primary biliary cirrhosis was 5% in Spanish patients with SS [37].

■ Mortality

One prospective study involving 261 patients with primary SS showed 11 patients died during follow-up [17]. The causes of death were lymphoma, pulmonary embolism, heart failure, vasculitis, and cerebral vascular accident. In this study, Skopouli et al. disclosed low C4 levels was main risk factor for mortality. By excluding the adverse predictors (low complement, cryoglobulinemia, lymphoma and so on), the mortality rate in patients with primary SS was identical to that of the general population.

Clinical examination

■ Salivary flow assessment

Sialometry is used to measure salivary flow into a calibrated tube for 15 min. When unstimulated salivary flow less than 1.5 ml/15 min, it is abnormal [4].

■ Salivary gland scintigraphy

The classification criteria for SS (based upon the 2002 criteria) includes positive salivary gland scintigraphy [38]. Compared with the previous invasive contrast sialography, salivary gland scintigraphy is a noninvasive procedure. It can reflect the salivary gland damage and function.

After Tc^{99} sodium pertechnetate intravenous injection, the salivary gland image can be graded from 1 (normal) to grade 4 (absence of the Tc^{99} intake). In the case of mild glandular impairment, it has difficulty differentiating normal from mild (grade II) when viewing salivary gland scintigraphy. If using grade III as the cut-off value, the sensitivity and specificity was 75 and 78%, respectively [39]. While using less than grade II, the sensitivity raised but specificity decreased. In our hospital, we still choose grade III as the positive salivary gland scintiscan.

To fulfill the diagnosis of SS (at least four positive criteria in 2002), salivary gland scintigraphy will be performed when the patient only has

three positive criteria. How to improve the sensitivity and specificity of salivary gland scan is becoming the key issue for the future.

■ Ultrasonography of salivary gland

The noninvasive procedures can demonstrate the decreased echogenicity and volume of submandibular glands in patients with primary SS. The sensitivity was 60% but specificity was 90% [40,41].

■ MRI & sialography

These noninvasive methods can be taken as diagnostic indicators. The abnormalities on MRI include nodular or dendritic pattern, cavities, ductal dilatation and so on [42].

■ Clinical significance of anti-Ro & anti-La antibody as well as other immunoglobulin subsets in primary SS

Anti-Ro (SSA) antibody is observed in 50–70% of patients with primary SS. Anti-La (SSB) is usually positive in 30–60% of SS patients [2,4,43,44]. Approximately 80% had positive antinuclear antibody and 40–50% were positive for rheumatoid factor. Cryoglobulinemia was noticed in 10% SS patients and low C4 in 5–13%.

However, the role of anti-SSA/Ro antibody in autoimmune diseases is controversial. In addition to SS, many immune diseases, involving systemic lupus erythematosus, rheumatoid arthritis (RA), myositis, scleroderma and even autoimmune hepatitis can present a positive anti-SSA antibody [44]. Further studies to determine the role of anti-SSA in the pathogenesis of SS are warranted. Another antibody that recently described to associate with neurologic involvement was antiaquaporin-4 antibody. The presence of this antibody is highly correlated with a distinct clinical phenotype, transverse myelitis or optic neuritis [45,46].

Previous studies demonstrated the SSA and SSB antibodies were associated with an early onset of the disease, glandular dysfunction and extraglandular manifestations [43]. Our previous study demonstrated that positive antibody or high grade of sialadenitis (biopsy) was strongly correlated with the intracellular adhesion molecule-1, matrix metalloproteinase-3 and TNF-related apoptosis-inducing ligand overexpression in salivary gland tissue [47].

One new antibody, anticyclic type 3 muscarinic acetylcholine receptor antibody peptides was identified by He *et al.* in primary SS, which may act as an autoantigen in the pathogenesis of SS [48]. Another antibody, antifodrin antibody, was also reported to associate with SS but not regularly tested clinically.

■ Positive Schimer's test or the Rose Bengal test

To identify the dry eyes or keratoconjuctivitis sicca, sterile filter paper strips are placed beneath the lower eyelid for 5 min. The Schimer's test is positive when the moistened length measure is less than 5 mm [2,4]. This test may not be reliable because pseudopositive or pseudonegative may be seen in some patients.

Another test to identify the dry eye is the Rose Bengal method, whereby the dye can stain the devitalized cornea and conjunctiva tissue. It may compensate for the insufficiency of Schimer's test, but is performed less routinely in the clinical practice. Other tests, including lissamine green test or fluorescein staining test, are considered due to the severe irritation the Rose Bengal method can cause [49].

■ Minor salivary gland biopsy

Salivary gland specimens obtained from oral surgeries were minced in 10% formalin and processed though paraffin embedding and sectioning. After hematoxylin and eosin (H&E) staining, the amount of lymphocyte infiltration was graded as 0, 1, 2, 3 and 4. Grade 0 is no lymphocyte, grade 1 is slight lymphocyte infiltration, grade 2 is moderate lymphocytes infiltration, grade 3 is one focus lymphocyte aggregation (>50 lymphocytes/ focus/ 4 mm^2) and grade 4 is more than 2 foci of lymphocyte aggregation [47,50]. Another classification for salivary gland biopsy is grade A (mild lymphocyte infiltration, less than one focus), grade B (moderate infiltration with one or more focuses) and grade C (form lymphoid follicles). More than one focus is considered abnormal [51].

Although many T lymphocytes are infiltrated in the salivary gland tissues, early study using thymidine (^{3}H) incorporation and transmission electron microscope demonstrated only a minor T cells *in situ* were blast transformed [52].

Disease activity index in SS

To evaluate the treatment outcome and disease activity in SS, two disease activity indices have been reported before. One is SS disease activity index (SSDAI) and the other one is Sjögren's systemic clinical activity index (SCAI) [53,54]. In 2010, a new disease activity index, the EULAR SS disease activity index (ESSDAI) was proposed. In total, 12 organ-specific domains, which contributed to the disease activity were enrolled [55].

Diagnosis

The classification criteria for SS in 1996 was originated from the assessment by European investigators [56]. A total of six criteria were classified:

- Ocular symptoms (> 3 months)

- Oral symptoms (> 3 months)

- Ocular sign (Schimer's test ≤ 5 mm/5 min, Rose Bengal Score ≥4)

- Minor salivary gland biopsy (≥ 1 focus)

- Salivary gland involvement (one of the following being positive):
  – Salivary scintigraphy
  – Parotid sialography
  – Unstimulated salivary blow, < 1.5 ml/ 15 min

- Autoantibodies (either Anti-SSA or anti-SSB positive)

Diagnosis of primary SS is established when a patient has at least four of the six criteria and without any underlying rheumatic or immune disease. Diagnosis of secondary SS is formed when the patient has an underlying rheumatic or immune disease plus the positive items 1 and 2 and any two from the items 3, 4, 5.

However in 2002, a revised version of the 1996 European criteria was proposed by the American–European Consensus Group [38]. It preserved all six items of 1996 criteria but revised the classification. For primary SS, it will be defined as follows:

- Patients need to satisfy four of the six criteria with at least one criterion being the presence of sialadentitis on lip biopsy or anti-SSA or anti-SSB. Other disease including hepatitis B or C, HIV infection, sarcoidosis and history of radiation should be excluded

- The presence of any three of the four objective criteria items (3, 4, 5 , 6)

For secondary SS, it was revised when patient has either item 1 or 2 plus any two among items 3, 4, 5.

Treatment of SS

Sjögren's syndrome like other autoimmune diseases, for example, scleroderma, does not have many positive and promising results using immunosuppressive medications for treatment of either oral dryness or systemic manifestations. Targeting therapy for T cells, B cells and macrophages did not prove the efficacy, although 60–70% of patients had antibody in the serum and many inflammatory cell infiltrations in the salivary gland. Many drugs including methotrexate, cyclophosphamide, leflunomide and cyclosporine have been used successfully in RA but not in SS [4,19,20].

Hydroxychloroquine has been used more frequently for SS but so far, it is proven to be effective in patients with arthralgia or fatigue. As no strong evidence to improve the dry eye and dry mouth, hydroxychloroquine monotherapy for SS is not recommended.

■ Management of keratoconjunctivitis sicca

The long dryness of eyes may cause discomfort and even ulcers. Long-term eye protection is necessary. The topical use of artificial tear solution or gel is recommended 3-times a day (t.i.d.) or four-times a day (q.i.d.). Preservative-free eye lotion is better when compared with the preservative-present artificial tear.

The most popular drugs at present for sicca syndrome belong to the class of muscarinic agonists. They can stimulate the muscarinic receptors which are a type of cholinergic receptors on the salivary gland or heart and smooth muscle, to produce tear or salivary fluid secretion. At present, there are two muscarinic agonists in the clinical use, pilocarpine and cevimeline [4,57,58]. In general, the result for oral fluid secretion that these two drugs generate is better than that of tear fluid secretion. Owing to the short half-life in these two muscarinic agonists, application at least t.i.d. are preferable for patients. However, the common adverse reaction (e.g., palpitation, sweating, general weakness, fatigue and so on) due to the muscarinic effect, limit its use in a regular dosage at the beginning particularly in Chinese patients. Pilocarpine can be started from 5 mg t.i.d. or q.i.d. Some patients may start from low dose (2.5 mg t.i.d. or q.i.d.) when they have side effects at doseage of 5 mg or higher. If pilocarpine 5 mg t.i.d. or 7.5 mg t.i.d. has no good effect, I will switch pilocarpine to cevimeline and *vice versa*. The contraindication to use muscarinic agonists is when the patient has glaucoma or active bronchial asthma.

■ Management of xerostomia

In cases with chronic xerostomia, patients may develop stomatitis, periodonitis, atrophic tongue, aphthous ulcers and dental caries. Good oral hygiene is absolutely necessary to minimize the dryness-associated oral complications.

In the majority of SS patients with xerostomia, either pilocarpine or cervimeline can significantly improve the symptoms. Two

randomized clinical trials have confirmed either pilocorpine 5 mg q.i.d. or cervimeline 30 mg t.i.d. could significantly increase the salivary flow rate or secretion [57,58]. As a matter of fact, these two drugs only relieve symptoms while they are administered. Interferon α has been tried in SS and showed an improvement in subjective oral or ocular dryness [59]. However, the anti-TNF-α therapy using infliximab in SS did not present any improvement in sicca symptoms [60]. A recent study by Strietzel *et al.* using an intraoral electrostimulation device could alleviate oral dryness and oral complications of xerostomia [61]. Unlike disease modified anti-rheumatic drugs (DMARDs) in RA, long-term adequate control of xerostomia by any specific drug including synthetic or biologic DMARDs has not yet been demonstrated.

■ B-cell-targeted therapy

Sjögren's syndrome involves many organs. Different treatment strategies are considered when different organs are involved. Since many synthetic DMARDs do not work effectively in SS, B cell-directed targeted therapy is considered because SS is an antibody-mediated lymphoprolifeative disorder.

Drugs that direct and indirect targeting B cells including chimeric monoclonal antibody to CD20 antigen (rituximab), humanized monoclonal antibody to CD20 (ocrelizumab), humanized monoclonal antibody to CD22 (epratuizumab) and humanized monoclonal antibody to BAFF (belimumab) have been used in recent years for treating SS patients with refractory exocrine disorders [21,62–66].

On average, relief of dry mouth by B-cell-depleting agents occurred in a certain percentage of patients, obviously noted in early primary SS. Some reports suggests that rituximab could improve the salivary flow rate and sicca symptoms but mostly were not run in randomized clinical trial. The anti-B-cell therapy also could reduce recurrent parotid gland swelling, fatigue and painful joints in four out of seven SS patients [21]. A long-term (36 week) open-label rituximab study in 16 patients with primary SS

showed after 12 weeks rituximab treatment, significant improvements were noted in the visual analog scale fatigue score, visual analog scale sicca-symptom score, tender joint count and short form 36 [63] .

Rituximab, can not only be used clinically in glands lesions, but can also be applied in extra- glandular manifestations of SS, for instance, ILD, CNS or peripheral neuropathy, renal involvement, and cutaneous vasculitis.

Another B-cell directed therapy, which has been used in RA or systemic lupus erythematosus, involves BAFF inhibitors (belimumab), which abolish the interactions of BAFF and their receptors. The clinical trials with anti-BAFF in primary SS are worth to be investigated [64].

To further evaluate the efficacy of those synthetic and biologic DMARDs in SS, large long-term, blind-label randomized clinical trial will be necessary in order to provide a better understanding of which drugs are useful in this common but difficult-to-treat immune disease.

Summary & future perspective

Sjögren's syndrome is an autoimmune disease with multiple organ involvement. Early diagnosis of SS has difficulty, especially in patients with negative serological tests or unavailable salivary biopsy specimens. To revise or establish a new classification criteria for early diagnosis of SS might be useful. Muscarinic agonists are useful mainly for salivary but less tear secretion. Therefore, the need to explore some new therapies is becoming an important issue to overcome this common but difficult-to-treat autoimmune disease.

Executive summary

- Dry eye and dry mouth are two common symptoms of Sjögren's syndrome. Extraglandular involvement may also occur, particularly pulmonary manifestations.
- Diagnosis of Sjögren's syndrome is based upon a revised version of European criteria in 2002.
- Muscarinic agonists are most popular drugs for Sjögren's syndrome. Other drugs including IFN-α, anti-TNF-α or B-cell targeted therapy are considered but efficacy is not confirmed yet.

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