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Sjogren's Syndrome: Strategies for Treatment

Arthur A.M. Bookman, MD, FRCPC

Introduction

Sjogren's syndrome, characterized by dry eyes, dry mouth, and immunological hyperactivity, has been one of the most difficult rheumatic diseases to differentiate and define. After many hours of consensus group development, studies on large cohorts/registries of over 1500 patients in totality and following national, European, American, and finally consensus iterations, criteria have been agreed upon for the classification of this disease. In the final analysis, these criteria are objective and accessible for measurement, and a number of them can be documented in clinical practice. To treat Sjogren's syndrome effectively, it is important to rely upon objective evidence with respect to the diagnosis of this disease, as well as the specific component of the condition that one is attempting to manage.

In this respect, Sjogren's syndrome is perhaps best confirmed by attempting to match the patient's findings with the 2016 ACR-EULAR Classification Criteria **(Table 1)**.[1] While these criteria are not meant for diagnosis but rather for the identification of confirmed cases for recruitment into clinical trials, they do exhibit a specificity of 95%, with a confidence interval (CI) of 92–97%, and a sensitivity of 96%, with a CI of 92–98%. It is important to note that high sensitivity is needed to correctly identify individuals with the condition. It is also important to note that many rheumatologists do not order a minor salivary gland biopsy and do not do a Schirmer's test or salivary flow rate. Patient history and physical examination along with a positive antinuclear antibody (ANA) and SSA (Ro) and/or SSB (La) accompanied by the presentation of dry eyes and mouth, may result in a clinical diagnosis of

Sjogren's syndrome being made, especially if there is Raynaud's phenomenon, gland swelling (parotids or submandibular) and/or leucocytoclastic vasculitis.

In clinical practice, many Sjogren's syndrome patients present with complaints of dry eye or dry mouth. One of the first questions that the practitioner must ask, is how reliable are these complaints? In our assessment of 385 patients with primary Sjogren's Syndrome,[2] we found that the correlation coefficient between the severity of complaints of dry eye measured by Visual Analog Score (VAS) and the measurement using the Schirmer's test was very poor at r=0.20. Correlation of these complaints with Rose Bengal or Lissamine Green staining for ocular surface dryness (van Bijsterveld Score) was even worse at r=0.18. It is important to keep in mind that correlation coefficients indicate more reliability as they approach r=1.

The classification of primary Sjogren's syndrome applies to any individual who meets the inclusion criteria, does not have any of the conditions listed as exclusion criteria, and has a score of >4 when the weights from the 5 criteria items below are summed.

Item	Weight/ score
1. Labial salivary gland with focal lymphocytic sialadenitis and a focus score of >1 foci/4 mm^2	3
2. Anti-SSA/Ro positive	3
3. Ocular Staining Score >5 (or van Bijsterveld Score >4) in at least 1 eye	1
4. Schirmer's test <5 mm/5 minutes in at least 1 eye	1
5. Unstimulated whole saliva flow rate <0.1 mL/minute	1

Table 1. American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome
Abbreviations: SSA/Ro, Sjogren's syndrome-related antigen A autoantibodies

Correlation of perceived dry mouth severity as measured by VAS with the measurement of unstimulated whole salivary flow was only marginally better at r=0.29. It may be of interest to note that even though the correlation was poor between perceived and measured dryness, in patients with Sjogren's syndrome, the correlation was significantly better than in patients without Sjogren's who had sicca complaints (controls).

This study demonstrates the importance of objective measurement in office practice rather than relying on patient complaints. In the office, a complaint of dry eye can be confirmed with a Schirmer's test and a complaint of dry mouth can be confirmed with unstimulated salivary flow. Saliva can be collected in a specimen cup for a 5-minute period. The sample is then quantified by aspirating the cup contents into a 3 mL disposable syringe with a 20-gauge needle. The volume of saliva produced should be expressed as millilitres per minute.

These aspects of the Classification Criteria can be performed in any outpatient setting. Furthermore, the ability to measure anti-SSA antibody levels in any community laboratory allows for the identification of a large proportion of patients without resorting to other subspecialists such as ophthalmologists or ENT specialists for confirmation. The Ocular Staining Score (or van Bijsterveld Score) and minor salivary gland biopsy must be performed by other specialists when the objective dryness and anti-SSA antibody test results are insufficient to meet the criteria. A single test is not sufficient to confirm a diagnosis.

Treating Dry Eyes

When treating dry eye, it is important to conduct the Schirmer's test first. If the Schirmer's test result is normal, then the complaint of dry eye is often due to meibomian gland dysfunction. These glands line the closure surface of the upper and lower eyelids where they meet. They secrete oil that forms a major sandwich layer of the tear film along with water, to ensure that liquid uniformly coats the cornea and the rest of the eye. With meibomian gland dysfunction, the tear surface becomes patchy, and the symptoms experienced are similar to those of dry eye. Obviously, the treatment for meibomian gland dysfunction differs from that of dry eye. Meibomian gland dysfunction needs to be confirmed by an eye specialist such as an optometrist or ophthalmologist. The eyelids can be examined with a slit lamp and the expression of oil with digital pressure to demonstrate the degree of clarity and function of the glands. Treatments

includes lid scrubs, hot soaks, and occasionally more advanced techniques such as 'Lipiflow'.[3]

For the patient who has an abnormal Schirmer's test result, the threat to the ocular surface is significant and can result in filamentary keratitis or punctate corneal ulceration. Initial treatment should of course include the use of artificial tears, by applying two drops in each eye on a regular basis, preferably four times a day. If artificial tears are used more than three to four times a day, then using preservative free preparations is preferable to prevent ocular irritation. Numerous artificial tear formulations are available, consisting of methylcellulose preparations, hyaluronate, polyethylene glycol, polyvinyl alcohol, glycerine and lacriserts. In fact, approximately 40 artificial tear preparations are available on the market.[4] There is no evidence for prioritizing these various formulations. Occasionally, dry eye is an issue during the night as well. Gel preparations can be helpful for these patients.

Some medical treatments for dry eye have been shown to provide benefit. For example, cyclosporin emulsion preparation can be applied topically. In a double-blind placebo controlled clinical trial,[5] treatment with cyclosporin emulsion provided benefit at a 0.05% concentration, administered as one drop in each eye twice daily. Cyclosporin emulsion preparation has been shown to improve the Ocular Staining Score at 3 and 6 months compared to placebo.[5] Another preparation, lifitegrast, a lymphocyte function associated antigen-1 (LFA-1) antagonist was also shown to provide benefit with significant improvement of fluorescein staining of the cornea at 84 days when compared with placebo.[6] This lymphocyte integrin inhibitor prevents T-cells from attaching to adhesion molecules on the cornea and inducing inflammation.

Varenicline, a smoking cessation tablet, was recently approved by the FDA in the United States in October 2021 as an aqueous nasal spray for treating dry eye. Varenicline is a highly selective nicotinic acetylcholine receptor agonist that binds with high affinity and selectivity at sites present on the trigeminal nerve within the nasal cavity. These receptors can mediate afferent signals in response to nasal stimuli, therefore, stimulating the lacrimal functional unit and producing tears. A 4-week trial that included 758 patients with dry eye has shown that treatment with varenicline demonstrated a significant improvement in the Schirmer's test result of 10 mm in the treatment groups ($p<0.0001$).[7] These participants had dry eye, and among them, a minority had Sjogren's syndrome. Minor side effects included sneezing immediately after the application of the spray, which was observed in 93.8% of the treatment groups.

If treatments such as artificial tears and topical medication are ineffective, more advanced topical measures can be considered. For instance, artificial tears can be created from the patient's own serum. To create the autologous serum tears, blood is drawn from the patient, spun down in a centrifuge to separate the blood components, then the serum is extracted from the sample and mixed with a preservative. The serum is then divided into aliquots and stored in a freezer at the patient's home. However, the vial of serum that is in use is stored in the refrigerator. A clinical trial has shown this treatment to be quite effective.[8] Platelet rich plasma is a variant of autologous serum tears, and is gaining recognition as an advanced treatment for patients with severe dry eye.[9]

> ***When artificial tears are insufficient to manage dry eye symptoms, other strategies can be considered.***

When artificial tears are insufficient to manage dry eye symptoms, other strategies can be considered. For example, punctal plugs can be inserted. Usually, punctal plugs are inserted into the lower eyelids alone, although in severe cases, plugs are inserted into the upper lid puncta as well. It is important that these devices be sized correctly by an eye specialist who has some experience inserting them. If the plugs are too small, they may fall out, and if they are too large, they may cause local irritation. Alternatively, the puncta can be cauterized, however, these orifices often re-cannulate.

Other treatment strategies exist. Enclosed spectacles can prevent tear evaporation and are practical and well tolerated for managing dry eye symptoms. These can be very efficient in alleviating symptoms for patients who want to read, work on a computer, or watch a video device. Inexpensive glasses to prevent tear evaporation include industrial working goggles or wrap around sunglasses. More attractive moisture guard spectacles can be purchased online and then taken to an oculist for the insertion of prescription lenses as indicated. Some eye specialists can provide these devices as well.

Scleral contact lenses are large ocular inserts with a purchase point on the sclera rather than the cornea. Lubricating liquid applied under these devices prior to insertion allows protection of the cornea and also provides a smooth refractory surface when filamentary keratitis or punctal erosion has caused corneal surface perturbation.

Treating Dry Mouth

Dry mouth can be more difficult to treat. Most patients are satisfied with sips of water. It is important to convey to the patient that a larger volume of liquid does not produce larger amounts of saliva. Indeed, over-consumption of liquid can result in nocturia and consequent disorganized sleep with resultant exhaustion. Sips of liquid should suffice. Gustatory stimulation is quite powerful in its ability to induce salivary flow. Sugar free candy or gum consumed throughout the day can be effective. In fact, any device in the mouth such as a button or cherry pit can induce the production of saliva. Lozenges are available that include adhesive that can be tacked onto the buccal surface of the patient's molar at bed-time, providing gustatory stimulation through the night.

There are many topical preparations that provide short-lived benefit to the sensation of oral dryness, but few give satisfaction greater than sips of water.

Salivary flow can sometimes be stimulated with parasympathomimetic preparations such as pilocarpine or cevimeline. In a 1999 double blind placebo-controlled trial, pilocarpine at 5 mg four times a day demonstrated a statistically significant improvement in unstimulated salivary flow at 12 weeks compared to a placebo.[10] Cevimeline is purportedly more specific for the salivary gland muscarinic 3 receptor with fewer patient complaints of sweating. A 12-week trial in which 197 patients with dry mouth received 30 mg of cevimeline three times a day demonstrated a significant improvement in the patients' assessment of global VAS compared to placebo.[11] However, the effectiveness of, and tolerance for, these preparations can be quite variable. Frequently reported complaints include sweating and urinary retention.

One must be aware of topical complications that arise from chronic oral dryness. Monilia overgrowth on the tongue, buccal membrane surfaces, and angles of the lips (angular cheilitis) can be managed with topical nystatin and/or ketoconazole. When monilia evolves to plaque formation or diffuse thrush, treatment with ketoconazole tablets at a dose of 200 mg daily for seven to ten days might be necessary. Often such overgrowth is recurrent, necessitating repeat courses of treatment as indicated.

Dental damage is another major issue associated with dry mouth. The pattern of decay observed with xerostomia is quite distinctive, with caries along the gingival margins, and pock-like fragmentation of the teeth. Incisors are ground down along the occlusive surface. The only conservative treatment with a modest proof of benefit is topical fluoride,[12] which can be applied locally on a regular basis in various forms, including the use of fluoride paint, fluoride gel trays worn for 30 minutes each night, or with a high fluoride concentration dentifrice used regularly. There is great concern over management with dental caps as decay frequently works its way into the root at the gum line. The success of dental implants in these patients depends on the status of the areolar ridge and the degree of gingival recession. A recent literature review assessed clinical outcomes of dental implants in patients with Sjogren's syndrome.[13] The review identified 19 studies for analysis totalling 712 implants placed in 186 patients; 705 implants were followed up for a mean of 72.5 months. The failure rate was 4.1% (29/705) at a mean time of 12.9 ± 31.7 months. The probability of failure was 2.8% (95% CI 1.6–4.1%). Hence, dental implants should be considered by dentists as a viable treatment option for patients with Sjogren's syndrome because the failure rate is fairly low. Patients may, however, experience a higher marginal bone loss around implants than patients from the general population. Intense regular maintenance (three times a year) with amalgam fillings in the molars and composite fillings along the gum line can ameliorate the rate of decay. Sterilization of the oral flora with chlorhexidine

rinse may be of benefit, however, this preparation does leave a brown stain on dental plaque.

Parotid Swelling

Parotid gland swelling is another complication reported frequently in patients with Sjogren's syndrome. This swelling can be painful and unsightly and is sometimes an indication of complications. Sjogren's syndrome begins with a ductal epithelial cell inflammation resulting in a highly deranged ductal drainage system, with areas of sialectasia and areas of ductal stenosis. The most common cause of intermittent parotid swelling is incomplete drainage of the salivary duct system. Once-daily massage of the gland can prevent gelification of pooled saliva with consequent plugging of the duct.

Glandular enlargement can occasionally be caused by infection. Such patients have fever, more severe pain, and more progressive symptoms. A parotid abscess may form. Management with antibiotics such as amoxicillin with clavulanic acid, clindamycin, or levofloxacin may be necessary. Abscess formation is rarely observed and requires surgical drainage.

The physician must always be aware that persistent swelling, new nodule formation, or evolution of regional lymph nodes can be possible signs of lymphoma. Such patients require thorough imaging as well as core or excisional tissue biopsy so that cells can be examined in situ with appropriate immune-peroxidase staining. Fine needle aspirate is usually inadequate for diagnosis.

Extraglandular Disease Management

Up to 40% of patients with Sjogren's syndrome experience extra glandular complications. These can include constitutional symptoms such as sweats, weight loss, lymphadenopathy, cutaneous vasculitis, peripheral neuropathy, interstitial pneumonitis, interstitial nephritis, and inflammatory arthritis. Such patients can be managed with traditional

Organ	Treatment standard	Later line treatment
Dry eyes	• Artificial tears and tear gel (methylcellulose) • Other eye drops (HydraSense, Systane, Hylo, Hylorunate, etc) • Anti-inflammatory drops (ex steroids) under direction of an ophthalmologist	• Cyclosporine eye drops (Restasis) • Lifitegrast (Xiidra) • Autologous serum • Surgery – blocking tear ducts • Pilocarpine, cevimeline • Occlusive glasses, contacs • Corneal graft
Dry mouth	• Water, water with sodium bicarb • More frequent dental care • Fluride trays • Biotene toothpaste • Sugar free candies • Moistir • Xylomelts	• Major dental work • Pilocarpine, cevimeline
Other Specific organ involvement (i.e. inflammatory arthritis, leukocytoclastic vasculitis, etc.)	• Hydroxychloroquine for specific indications • Azathioprine, Methotrexate, • Leflunomide • Glucocorticoids	• Biologics • Rituximab • Clinical trials • Possibly in future Dazodalibep

Table 2. Organ-specific treatment approach; courtesy of Arthur Bookman, MD; courtesy of Arthur A.M. Bookman, MD, FRCPC

immunosuppressants including corticosteroids, azathioprine, methotrexate, and mycophenolate.

Recently, a number of clinical trials have been conducted to evaluate the benefit from targeted biologic agents for the treatment of Sjogren's syndrome. A Novartis phase 2B double blind placebo-controlled trial examining the safety and preliminary efficacy of iscalimab,[14] an Fc silenced, fully human monoclonal CD40 antibody has recently concluded (TWINSS core study). Patients who received iscalimab demonstrated improvement in the European Sjogren's Syndrome Disease Activity Index (ESSDAI) score over 24 months. One secondary measure was unsimulated salivary flow, which also demonstrated improvement. There was also a trend toward an improved patient reported outcomes score European Sjogrens Syndrome Patient Reported Index (ESSPRI).

Novartis is currently engaged in another phase 3 trial of ianalumab, a monoclonal B-cell activating factor (BAFF) receptor antagonist which also depletes B-cells through antibody dependant cellular cytotoxicity. A phase 2B trial evaluating the safety and efficacy of ianalumab in patients with Sjogren's syndrome[15] has reported very promising results, showing a dose-related decrease in disease activity. Other agents are being evaluated in early-stage trials, including dazodalibep,[16] which is under development by Horizon Therapeutics. Dazodalibep is a CD40 ligand antagonist that blocks T cell interaction with CD40-expressing B cells, disrupting the overactivation of the CD40 ligand co-stimulatory pathway. A phase 2 study evaluating dazodalibep has demonstrated benefit and a phase 3 trial is underway.

Deucravacitinib (Bristol Myers Squibb) is a TYK2 inhibitor that leads to interferon inhibition. This drug has shown promising results.[17] Deucravacitinib has bypassed phase 2 studies in Sjogren's syndrome and has been launched into a phase 3 trial that is currently underway primarily in the United States.

The field for therapeutics of Sjogren's syndrome is finally making some progress. Rheumatologists need to be the coordinators for managing this condition that has such disparate manifestations. This requires developing familiarity in areas that do not usually fall into our realm of management, such as dental care, ocular complications, and salivary gland inflammation **(Table 2)**. Aside from developing a systematic approach to this disease, it is also helpful to engage a cadre of colleagues from other specialties who are open to communication and are interested in developing added expertise in managing Sjogren's syndrome.

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