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Review Article

Dry eye disease associated with Primary Sjogren syndrome: An update

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ABSTRACT

Primary Sjögren's syndrome (pSS) is a chronic, multisystem autoimmune disorder, characterized by mononuclear infiltration of exocrine glands and other organs, resulting in dry eye, dry mouth and extra-glandular systemic findings. Primary Sjögren syndrome is of particular interest to ophthalmologists as it constitutes an important differential diagnosis in conditions with dry eye disease. The ocular tests are of great importance for diagnosis and monitoring of primary sjogren's syndrome. Also a better understanding of immunological mechanisms and molecular pathways have resulted in discovery of new therapeutics for local and systemic treatment. This article illustrates an update regarding pathogenesis, diagnosis, investigative procedures and treatment options for dry eye related to Sjogren's syndrome.

1. Introduction

Sjögren's syndrome (SS) is a chronic, multisystem, complex autoimmune disorder, characterized by mononuclear infiltration of exocrine glands and other organs. The clinical features of SS either present alone as a primary condition known as primary Sjogren's syndrome (pSS) or it can also be associated with other autoimmune disease like rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis.[1] The salivary glands and lacrimal glands are the main targets of the autoimmune mediated chronic inflammation leading to glandular destruction and atrophy. Dryness of mouth (xerostomia) and dry eye (keratoconjunctivitis sicca) are the main symptoms of pSS. Patients may have other systemic manifestations like fatigue and migrating muscular and joint pain[2,3] and small fiber neuropathy (SFN), presenting as paraesthesia, allodynia and burning sensation.[4] The pSS is a complex disease, with an unclear pathogenesis. The genetic predisposition and environmental triggers may lead to development of pSS. The diagnosis of Sjogren's syndrome is challenging due to heterogeneity of manifestations and lack of definitive diagnostic tests.

Dry eye disease (DED) also known as keratoconjuctivitis sicca (KCS), is the most consistent feature of Sjogren's syndrome limiting the persons activity and affecting quality of life (QOL). According to International Dry Eye Workshop, DED is defined as a multifactorial disease of the tears and ocular surface characterized by loss of tear volume and tear film instability with damage to ocular surface which result in symptoms of discomfort and visual disturbance.[5,6] The onset of the disease is frequently insidious with vague symptoms over many years, resulting in delayed diagnosis in majority of the cases of pSS.[7]

This review provides an update on recent concepts in pathogenesis of pSS, diagnostic tools & biomarkers for early diagnosis and recent advances in management of DED in pSS.

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2. Epidemiology

Sjogren syndrome is one of the most common autoimmune disorder of adults, affecting about 4% of the general population.[8,9] The SS is found in every part of the world. The epidemiological risk factors of SS are female sex and first grade relatives with an autoimmune disease.[10] There is a female preponderance with female to male ratio of about 10.72.[8,11] It can occur in all age groups but commonest age group is 40-60 years. Ocular and oral dryness is the characteristic feature of Sjogren's syndrome and is seen in more than 95% of the patients.[12,13] It has been reported that about 10% of patients with significant dry eye have underlying Sjogren syndrome.[14–16] About 85% of SS patients have severe or very severe DED.[17]

3. Pathogenesis of Sjogren's Disease and DED

The etiopathogenesis of SS is still not well studied and understood but it is assumed to be multifactorial disorder.[18,19] It is hypothesized that the etiopathogenesis of SS involves four events which are as follows: (1) initiation by an exogenous factor; (2) disruption of epithelial cells of exocrine glands (salivary, lacrimal) (3) T lymphocyte migration and lymphocytic infiltration of exogenous glands; (4) B lymphocyte hyper-reactivity and production of rheumatoid factor and antibodies to Ro(SS-A) and La(SS-B).[19,20] The lymphocytic infiltrates interfere with the normal glandular function by cell mediated destruction of glandular structures, release of cytokines & interferons (IFN-α) and production of autoantibodies.

The cellular and molecular processes responsible for DED in SS are increased inflammatory cytokines, increased matrix-metalloproteinases and activation of immune cells.[21]

3.1. Sex hormones

There is strong female to male predominance of SS that means there are sex specific factors which predispose to SS. While the androgen is assumed to be protective, the estrogen on contrary is causative factor in autoimmunity. The incidence of SS peaks around menopause which is marked by fall in levels of estrogen. From this it is deduced that the absolute level of estrogen is not as important as the change in ratio of androgen and estrogens.[22] It is seen that cysteine-rich secretory protein 3 (CRISP-3), an androgen responsive salivary protein that is upregulated by DHEA, is expressed at lower levels in salivary glands of patients of Sjögren's syndrome, and it has lost its polarized organization in the acini, even in regions without inflammatory cells.[22,23] Sex hormone is responsible for maintenance of normal ocular surface integrity and meibomian gland function. Post-menopausal decrease in estrogen results into inflammation of glandular tissue and disruption of ocular surface.[24]

3.2. Genetics

Genome wide association study (GWAS), has detected correlation between HLA, IRF5, STAT4 and BLK genetic loci, loci at IL-12A and CXCR5 regions and Sjogren's syndrome.[25,26] The HLA correlation was found to be stronger in the subsets with anti-Ro and anti-La positivity.[26] Other studies also revealed strong genetic association of pSS with EBF1, FAM167A-BLK and TNFSF4 and CHRM3 genes.[27,28]

3.3. Viral triggers

A ubiquitous virus is assumed to play role in the causation and etiopathogenesis of SS but till now there is no definite evidence of any particular viral infection to be causative and till date the identity of any such virus remains elusive.[26]

The viruses which have been implicated are cytomegalovirus (CMV), Epstein-barr Virus (EBV), human herpes virus -8 (HHV-8), hepatitis C virus, human T-lymphocyte virus type and Enterovirus.[26] Viral infections have been proposed as external "triggers" for development of autoimmune disease pSS. An increase in production of interferons (IFN) reflects that there is increased antiviral response.

3.4. Autoantibodies

The presence of autoantibodies against SSA/Ro and SSB/La is characteristic of Sjogren's syndrome but its role in disease pathogenesis is not well understood. In patients with Sjogren's disease anti-Ro/SS-A, anti-La/SS-B and antinuclear antigens (ANA) are detected in high level which forms the basis of its diagnosis. Interestingly, autoantibodies can be used for discriminating between Sjogrens syndrome associated KCS versus other causes of aqueous-deficient dry eye. Anti-Ro and Anti-La anti bodies are only detected in patients of Sjogren's disease associated KCS.[29,30] Ro-52, also known as TRIM21 plays an important role in anti-viral and other innate responses including cellular proliferation and apoptosis.[26] It has good affinity with Fc portion of IgG, by virtue of which it binds to antibody coated virus particles and subsequently degrade them via proteasomal complex.[26,31] Ro-52 inhibits the production of bcl-2 hence causing increase in apoptosis.[26–32] Ro-60 is believed to have a role in repair of intracellular damage following UV radiation.[26,33] La by binding to pre-miRNA increases its stability and thus prevents its degradation by nucleases.[26,34] La mediates RNA interference and also exhibits antiviral actions.[26,35]

3.5. Role of interferon in DED associated with pSS

On the basis of vast array of clinical presentation and pathological findings it is assumed that IFN expression pattern will vary among individuals and the systemic IFN

type I and type II signature will influence the severity of disease.[36–39] IFN-γ is the key interferon involved in most of the pathways that have been identified in the pathogenic processes of Sjogren's syndrome.[29] It has been suggested that genetic associations of SS include, interferon regulatory factor-5 (IRF-5) and the IFN signalling pathway.[36–38,40] IL-1β and IFN-γ play a pivotal role in squamous metaplasia of the ocular surface epithelium in response to chronic inflammation.[36] Th1 cells and NK cells infiltrate at the ocular surface and release IFN-γ during the process of squamous metaplasia and as result of which both the cytokines are seen at the ocular surface in dry eyes.[36,41]

4. Ocular Involvement in pSS

Lacrimal gland is most commonly affected by immune mediated inflammation in pSS. The most frequent clinical presentation of pSS is dry eye or kerato-conjuctivitis sicca (KCS).[41,42] It has been reported that density and function of sensory nerve terminals (afferent) responsible for tear reflex are reduced in pSS as compared to healthy individuals.[43,44]

Ocular signs and symptoms are represented by surface disorders with varying severity and grades.The common complaints with which patients present are foreign body sensation, reduced or increased tearing, itching and blurring of vision.[6] The slit lamp examination reveals redness, conjunctival keratinization with chalasis, and punctate or filamentous keratitis.[41–46] Other ocular manifestations of pSS which have been reported include episcleritis/scleritis, uveitis, retinal vasculitis, cicatrizing conjunctivitis, sterile corneal ulcer/infiltration, corneal melting perforation and optic neuritis.[47]

5. Diagnosis of Dry Eye Disease Associated with pSS

5.1. Symptom evaluation

Various questionnaires have been used for the evaluation of symptoms. The Ocular Surface Disease Index is a commonly used questionnaire method consisting of total twelve questions for assessment of dry eye symptoms. Through this questionnaire, it is possible to differentiate between the normal subjects and the ones having dry eye disease, simultaneously the severity of the eye symptoms is measured and their effect on vision is also gauged.[7] MDEIS (Mc Monnies dry eye questionnaire) was designed as a screening tool to differentiate patients of dry eye disease from those who are normal and it was based on the specific symptoms of dry eye whether they were present or not.[48,49] Besides these, other questionnaire methods have also been developed like the Symptom Assessment In Dry Eye (SANDE) and Dry Eye Questionnaire. SANDE consists of two visual analogue scales for assessment of the frequency and severity of dry eye syndrome[50] while Dry Eye Questionnaire consists of four variables for measuring several symptoms based on the intensity of symptoms in the morning, late in the day, degree of irritation and frequency.[7,51]

5.2. Test for tear film function

Schirmer test is a standard assessment method for determining adequate amount of aqueous tear production.[7] The Schirmer test 1 is performed with anaesthesia and measures baseline aqueous tear production and Schirmer test 2 is performed without anaesthesia is used for measuring reflex tear production in the eye.[52]

5.3. Tear breakup time (TBUT)

Tear film instability is an important sign of dry eye disease and it is commonly determined by TFBUT. In TBUT we measure interval between instilling topical fluorescence and appearance of first dry spot on the cornea and is an indicator of tear film stability and this test is commonly used in the assessment of dry eye disease.[52]

5.3.1. Tear film osmolarity

Increased osmolarity of the tear film is one of the most characteristic feature of dry eye disease. The methods which were being used for the measurement of tear film osmolarity were laborious and time consuming but with the availability of an in-office instrument for determining tear film osmolarity, it has resulted in more swift clinical application of such technology.[42,53] A new tear osmometer has been approved by the FDA for marketing in the United States.[42,54] Tear film osmolarity has a positive predictive value of 86% in the diagnosis of dry eye disease which is highest of all the available objective tests.[53,54] Dry eye patients have increased tear film osmolarity.[54,55]

5.3.2. Tear film composition

Tear film contains various types of immunoglobulins, antibacterial and anti-inflammatory chemicals.[6] Inflammatory mediators are also present in the tear film and their level useful in assessing the role of inflammation in dry eye disease and is also helpful in measuring severity of dry eye disease. The activity and production of matrix metalloproteinase (MMP)-9 is increased in dry eye disease and other ocular surface disorders.[42,55] Estimation of pro-inflammatory cytokines and chemokines (interleukin & tumor necrosis factors) in tear fluid can be diagnostic. High level of IL-1α, IL-6, IL-8, TNF- α and transforming growth factor (TGF)-β1 RNA transcripts have been reported in conjunctival epithelium of Sjogren's syndrome as compared to healthy controls.[56]

5.4. Test for epithelial integrity:

Staining of the ocular surface is a vital aspect of grading DED.[57–59] Measurement of the epithelial integrity of the ocular conjunctiva can be evaluated by Lissamine green test

or rose Bengal test and that of cornea by fluorescein staining and this is more reliable to evaluate keratoconjunctivitis sicca.[60,61] Both dyes - rose bengal and lissamine green, primarily stain epithelial cells, keratinized cells, goblet cells, and devitalized cells. Rose Bengal dye is the dye of choice for grading conjunctival damage in patients with KCS.[52] Interestingly, this is not a true vital dye and is very toxic to epithelial cells, particularly in case of KCS in which the shielding function of the preocular tear film is also weakened.[52,62] This dye becomes so irksome that many investigators indorse instillation of a topical anaesthetic prior to carrying out this test.[52,63] This is in direct contrast to Lissamine green dye ; a true, non-irritating vital dye.[39,52] Fluorescein dye is also non-toxic and non-irritating and is very useful dye for staining those areas of the cornea where the epithelium is eroded or absent and for staining precorneal tearfilm.[52,64]

The tear breakup time, in conjunction with Ocular Surface Disease Index and corneal fluorescein staining is the best approach to differentiate Sjogren's syndrome from other causes of DED.[7,65] The frequent use of tear flow and volume testing is important as SS related DED is considered to be a disease of reduced tear flow, secondary to inflammation of lacrimal glands.[59]

5.5. Imaging techniques

Meibography is specialised illumination and observation technique to observe the Meibomian gland morphological structure. Impairment of function of Meibomian gland as weighed by infrared meibography is reported in case of pSS.[7,66] It has been reported that meibomian gland dropout of the upper eyelid was more obvious in SS subjects than in non-SS subjects.[67] MRI and CT scans are useful in differentiating benign from malignant lesions when the patients present with unilateral enlargement of lacrimal gland. MRI may be recommended to measure inflammation, glandular size and fat deposition. Risk of B-cell lymphomas in pSS is increased significantly and rarely they tend to occur in the lacrimal gland.[68] The glandular involvement in pSS can be assessed by salivary gland ultrasonography.[69]

5.6. Histopathological finding of lacrimal gland

Lacrimal gland biopsy is usually obtained from the palpebral part of the gland under local anaesthesia. Performing biopsy of lacrimal gland is technically more challenging than the biopsy of minor salivary glands (MSGs) as there is a risk of perioperative bleeding and injury to secretory ducts. Histopathological studies of lacrimal glands in pSS patients are rare owing to technical challenges and risk of complications.[7] There is aggregation of lymphocytes mostly T helper cells and B cells and the destruction of tubulo-acinar morphology of lacrimal gland tissue in SS is secondary to lymphoproliferation of B cells and T helper cells. Infection of lacrimal gland tissue with EBV may play a role in the etiopathogenesis of the SS in some selected cases.[7,70]

5.7. Role of CATHEPSIN-S (CTSS) as biomarker for Sjogren's syndrome for dry eye

It has been suggested that tear CTSS activity in patients of SS is significantly increased as compared to other healthy subjects or in patients where cause of dry eye disease is not SS or any other autoimmune disorder, suggesting it may be used as a novel biomarker for SS.[71] Although tear CTSS activity was significantly raised in both primary and secondary SS, it was statistically more strong in differentiating patients with SS from a general population of patients with autoimmune disease than from a population of patients with sicca or nonspecific dry eye disease[71] proposed the inhibition of Cathepsin S (CTSS) in male NOD mice as a potential therapeutic approach of pSS ocular manifestations. Their study revealed that systemic intraperitoneal administration of the peptide-based inhibitor, Z-FL-COCHO (ZFL) significantly decreases activity of CTSS in tears, lacrimal glands and spleen, as well as the total number of lymphocytes invading the lacrimal glands resulting in increased stimulation of tear secretion.[72,73]

5.8. Role of novel autoantibodies in diagnosis of dry eye disease in Sjogren's Syndrome

In the DREAM (Dry eye assessment and management study) study it was found that participants with SS had a significantly higher prevalence of SP-1 autoantibodies as compared with those without SS or other autoimmune diseases.[74] It was also seen that those patient who were positive for this novel autoantibodies alone or along with the traditional anti-Ro and anti-La antibodies had worse corneal and conjunctival staining indicating that the dry eye disease was more severe in comparison to those who were negative for either autoantibodies.[74] This indicates that these novel autoantibodies may be a marker of more severe ocular surface disease in those who are positive for traditional SS antibodies.[74] Moreover in mouse model of the disease pathogenesis it was seen that SP-1 autoantibodies were detected in the early course of disease.[74,75] Thus early detection along with severity of disease can be done with the use of these autoantibodies. Early detection of SS has got implication in initiating early treatments to relieve symptoms and to enable monitoring for systemic complications.[74] In addition, patients who commence treatment within the first 5 years of disease onset may be more likely to respond to treatment and have better future prognosis as compared to those with delayed initiation of therapy.[74,76–78]

6. Importance of Ocular Parameters in Classification of Sjogren's Syndrome

Till today, we do not have any such parameter which can serve as 'gold standard' for diagnosis and classification of SS including clinical, laboratory, pathological or radiological characteristics.[2] In 2002, a revised international classification of SS was established by the American-European Consensus Group.[79] The ocular components which are being used for defining SS include two objective measures of ocular involvement, i.e., a Schirmer I test result ≤5 mm in 5 minutes and a Rose Bengal or other ocular dye score ≥4 according to van Bijsterveld scoring system.[79,80] The most recent and new American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) classification criteria for primary Sjögren's syndrome are consequences of an international collaboration and have been deduced using a well-established and validated methodology. However, these new classification criteria do not differentiate between primary and secondary Sjögrens's syndrome.[2] The inclusion criteria for this classification pertaining to ocular involvement are any patient with at least one symptom of ocular dryness, defined as a positive response to at least one of the following : (i) Have you had daily, persistent, troublesome dry eyes for more than 3 months? (ii) Do you have a recurrent sensation of sand or gravel in the eyes? (iii) Do you use tear substitutes more than three times a day.[81] The criteria used include three objective measures of ocular involvement i.e. ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) in at least one eye, Schirmer's test ≤5mm/5 min in at least one eye, Unstimulated whole saliva flow rate ≤ 0.1 ml/min.[78]

7. Management of Dry Eye Diseases in Sjogren's Syndrome

The treatment of dry eye disease is mainly symptomatic and this includes replacement therapy, local stimulators of tear secretion and anti-inflammatory agents besides the supportive surgical procedures.[82] Moreover general preventive measures need to be taken including avoidance of medications that aggravate ocular dryness (e.g. anticholinergics, antihistamines, and diuretics) and irritants such as cigarette smoke and dust.[82,83] The advice should also be given for maintenance of a humid environment by the use of spectacles with side shields and taking intermittent breaks while studying.[82,83] In general, this can be concluded that the treatment is built upon the severity of the dry eye disease and the response of patients to such treatment.[42]

7.1. Topical tear substitutes and lubrication:

First-line treatment of dry eye disease in SS includes lubrication with tear substitutes followed by anti-inflammatory eye drops. Till today none of the tear substitutes are considered superior and finding suitable tear substitute is very individualised and is based on trial and error method.[7,42,84] All the lubricants vary in their properties like viscosity, lipid constituent and level of hydration. Active ingredients include hydroxypropyl methylcellulose, carboxy methylcellulose, polyvinyl alcohol, hyaluronic acid, and liquid polyols.[7,85] Tear drops that are more viscous provide longer relief but are associated with problems of blurred vision and discomfort. Ophthalmic inserts containing for example hydroxypropyl methylcellulose can be used if the patients want tear drop which provides prolonged relief.[7,86] Preservatives which are being used in tear substitutes have got adverse effects on the ocular surface.[21] Benzalkonium chloride and EDTA are potentially harmful to the surface of eye especially when the cornea is dry and such tear drops are used for longer duration.[42] The deleterious effect of preservatives increases with its frequent use and in dry eye disease patients due to decrease in tear volume they are more prone to develop toxicity from preservatives used in tear drops. Therefore, whenever supplemental tear drops are used more than 4-6 times a day, preservative free tear substitutes are recommended.[42]

7.2. Anti-inflammatory therapy

Anti-inflammatory drugs are recommended for patients having moderate to severe dry eye disease in cases of Sjogren's syndrome.[42]

7.2.1. Topical corticosteroids

Topical glucocorticoids such as dexamethasone, methylprednisolone and fluorometholone eyedrops reduce inflammatory cytokine expression and many studies including several RCTs have shown improvement of ocular surface parameters after short term use in dry eye patients.[87,88] A major limitation of their use are side-effects particularly the increased pressure of the eyeball, formation of cataract, and risk of infections in case of severe dry eye. Therefore, they are usually limited to short-term use (2–4 weeks).[89]

7.3. Topical cyclosporine

Cyclosporine inhibits the calcineurin-dependent events in T-cells thereby affecting both cellular and humoral mediated immunity, ultimately inhibiting the release of proinflammatory cytokines.[7,89] Topical Cyclosporine is available in 0.05% and 0.1% concentration and they usually take weeks of administration for their therapeutic effect to occur. Topical cyclosporine has a limited clinical use because of its poor tolerance by the patients which results due to its reported discomfort upon topical use and relatively long duration of treatment required.[7,88] There is

improvement in corneal and conjunctival staining scores along with Schirmer's tear test results after the use of topical cyclosporine. There is also marked decrease in blurred vision score among the subjective outcomes in the patients using topical form of cyclosporine.[82] Besides the improved clinical outcome, there is also improvement in the immuno-histology of the ocular surface with topical cyclosporine therapy including decrease in cell surface markers of activated T-lymphocytes and apoptotic cells in conjunctival biopsies.[42,90,91] The usually recommended therapy is topical application of one drop of cyclosporine in each eye two times a day.[42,92]

7.3.1. Omega-3 essential fatty acids

In the category of anti-inflammatory treatment for dry eye disease essential fatty acids particularly omega -3 fatty acid is also considered on the virtue of its anti-inflammatory action.[42,93] and based on its anti-inflammatory property omega-3 fatty acid intake has been recommended for patients with dry eye disease.[42,93] The essential fatty acids must be taken from dietary sources as the body cannot synthesize them. Omega -3 fatty acid cannot be taken > 3mg. High dose could cause excessive bleeding in some patients.

Lifitegrast (Xiidra®) is approved by the FDA as the first new DED drug after a long time.[7,94] Lifitegrast works by blocking the interaction between intercellular adhesion molecule-1 and lymphocyte functional associated antigen-1, which is critical for the migration of antigen-presenting cells to the lymph nodes as well as CD4+ T cell activation and migration to the ocular surface.[7.97] Several clinical trials have showed an improvement in dry eye signs (staining) and symptoms for lifitegrast 5% ophthalmic solution and a good safety profile.[7,88,95–97] The advantage of lifitegrast as compared to cyclosporine is its quicker time of action: symptoms improved with lifitegrast in only 14 days.[88]

7.4. Secretagogues therapy

7.4.1. Pilocarpine

The pilocarpine tablets benefit for ocular symptom of SS has been demonstrated in two RCTs that recruited 373 and 84 patients respectively, For 12 weeks at doses of 10 or 20 mg daily.[83,98,99] In one of the study, 42% of patients taking 20 mg pilocarpine daily reported global improvement in the symptoms of dry eye as compared with 26.1% of patients taking placebo ($P < 0.009$).[98] The other study showed that pilocarpine was superior to artificial tear use or punctal occlusion in terms of subjective global assessment of dry eye symptoms. Sweating (43.3%), headache (15.8%), flu symptoms (14.2%), nausea (11.8%), and rhinitis (10.2%) were some of the adverse effects reported in patients receiving 20mg/day of pilocarpine.[98] Arimoto et al. reported excellent result of topical Rebamipid in autoantibody positive Sjogren's syndrome having mucin deficiency due to loss of goblet cells.[100,101]

7.4.2. Diquafosol

Diquafosol is available as an ophthalmic solution in 3% concentration. It stimulates the secretion of water and mucin by its action on $P2Y_2$ receptors on the conjunctival epithelial and goblet cell membrane.[88] Several RCTs have exhibited improvement in signs and symptoms of dry eye, including in SS patients.[88,102–104] In the USA, however, 2% diquafosol tetrasodium failed to get FDA approval because endpoints were not achieved.[105]

7.4.3. Cevimeline

The oral use of cevimeline for the treatment of dry eye and dry mouth in patients with SS has been demonstrated in many clinical trials.[82] Improvement in global assessment of dry eye symptoms with doses of 20 mg to 30 mg three times per day was seen in many studies.[82]

7.5. Punctal occlusion

It is the procedure where the tear drainage system is blocked at the level of the puncta or canaliculus and it helps to preserve ocular surface tears or instilled artificial tears.[42] Punctal plugs, synthesized of either silicone or dissolvable collagen, use has shown improvement in symptoms, decrease staining scores, increase in tear break-up time and increase in the number of goblet cells.[82,106] The high rate of loss of around 29% of plugs within 1 month after application or approximately 50% of plugs at any point of time was the main disadvantage with their use.[82,106,107] Other complications include epiphora and conjunctival erosions.[82,107]

7.6. Autologous serum

The autologous serum contains substances such as epidermal growth factor, transforming growth factor β, fibronectin and vitamin A, which are generally present in normal tears but are not found in tears of patients with keratoconjunctivitis sicca. Hence, it is used as the topical treatment of dry eye.[82] Topical autologous serums are used to treat serious cases of dry eye disease that have not shown improvement to other treatments, including intensive lubricant and anti-inflammatory therapy.[42] The disadvantages of using autologous serum consist of the tideous process of preparation, the need to refrigerate the eye drops and moreover the potential risk of infection if contamination of the solution occurs.[42,108] The stability of frozen autologous serum has been verified, however, for up to 3 months.[42,109] Typically, the serum is applied topically four times daily, and this can be done in conjunction with other therapy.[42]

7.7. Mucolytic therapy

Mucolytic acetylcysteine eye drops may help in treatment of filamentary keratitis of SS, in which strands of degenerated epithelial cells and mucus (filaments) are attached to the cornea.[88] Early studies including a RCT versus normal saline eye drops showed improvements in moderate-to-severe dry eye with a once daily instillation.[88,110–112]

7.8. Therapeutic contact lens

Scleral lenses rest on the sclera, and create a fluid-filled chamber over the affected cornea, which has proven to be an attractive option for aqueous deficient dry eye.[88] Several silicone-hydrogel soft contact lenses are FDA approved for therapeutic extended wear and such contact lenses also provide relief in the discomfort and blurring of vision in primary and secondary Sjögren's disease.[42,113]

7.9. Eyelid management

The expression of the meibomian glands by using two cotton-tipped applicators pressed together to compress the eyelid is commonly performed in patients with meibomian gland dysfunction.[42,114] The substitute method is simultaneous digital pressure application on the skin and cotton-tipped applicator and pressure on the palpebral conjunctiva so as to compress the gland without risking trauma to the globe.[42,114] The continuous controlled thermal compression (Lipiflow System) device has been recently approved by the FDA, which liquefies the meibomian gland secretion and then expresses the material.[42,115,116] The botulinum toxin injection has been used in cases where full closure or partial closure of the eyelid is indicated for short period of time[42,117] The surgical options such as tarsorrhaphy may be considered to manage the eyelid and degree of exposure of the ocular surface when other measures fail.[42]

8. Summary

One of the most quality of life and activity-limiting feature of Sjogren's disease is dry eye disease. For symptoms evaluation we can use number of questionnaires to grade severity of symptoms and better understanding of the stage of disease. A number of clinical tests of tear function can be performed in the OPD setting to quantify the volume and stability of tear function. Also, evaluation of the severity of dry eye disease can be done with application of topical dyes, including fluorescein, rose bengal and lissamine green, to quantify damage to the ocular surface. Tear film osmolarity is one of the advanced technique for diagnosis of dry eye and it can also be used to monitor response to therapy.

The nature of the dry eye and severity of symptoms play important role in the management of dry eye. In early stages of the disease, tear replacement with topically applied artificial tears or lubricant solutions may be sufficient but in cases of progressive or more severe KCS, it requires use of dietary supplements (omega 3 essential fatty acids), anti-inflammatory measures (e.g., topical corticosteroids or cyclosporine), or oral secretagogues. Once the inflammatory component of dry eye is controlled plugging of lacrimal puncta can be done. Topical or systemic doxycycline therapy is required for treatment of lid margin (meibomian gland) disease. Topical autologous serum or partial closure of the interpalpebral fissure to reduce surface exposure can be used in cases of most severe dry eye particularly in cases which are unresponsive to standard therapy. Scleral contact lenses may be needed to control severe ocular surface damage. Often patients need multiple treatment options, especially in more severe dry eye such as with SS, and not uncommonly patients fail to improve at all despite the numerous treatment options available.

DED related to SS remains a challenge, in part due to its multifactorial nature, the poor correlation between symptoms and signs and the multiplicity of treatments which have not been compared in randomised clinical trials. Despite this, knowledge of the pathophysiology of dry eye is increasing exponentially in recent years and there are a range of new treatments emerging, giving hope that more effective therapeutic options are on the horizon.

9. Source of Funding

None.

10. Conflict of Interest

None.

References

1. Theander E, Jacobsson LTH. Relationship of Sjögren's Syndrome to Other Connective Tissue and Autoimmune Disorders. *Rheum Dis Clin North Am*. 2008;34(4):935–47. doi:10.1016/j.rdc.2008.08.009.
2. Jonsson R, Brokstad KA, Jonsson MV, Delaleu N, Skarstein K. Current concepts on Sjögren's syndrome – classification criteria and biomarkers. *Eur J Oral Sci*. 2018;126(S1):37–48. doi:10.1111/eos.12536.
3. Jonsson R, Vogelsang P, Volchenkov R, Espinosa A, Wahren-Herlenius M, Appel S. The complexity of Sjögren's syndrome: Novel aspects on pathogenesis. *Immunol Lett*. 2011;141(1):1–9. doi:10.1016/j.imlet.2011.06.007.
4. Cafaro G, Croia C, Argyropoulou OD, Leone MC, Orlandi M, Finamore F, et al. One year in review 2019: Sjögren's syndrome. *Clin Exp Rheumatol*. 2019;37(118):3–15.
5. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II Definition and Classification Report. *Ocular Surf*. 2017;15:276–83. doi:10.1016/j.jtos.2017.05.008.
6. Maurya RP. Dry eye disease: An overview. *Ind J Clin Exp Ophthalmol*. 2018;4(4):433–4.
7. Bjordal O, Norheim KB, Rødahl E, Jonsson R, Omdal R. Primary Sjögren's syndrome and the eye. *Surv Ophthalmol*. 2020;65(2):119–32. doi:10.1016/j.survophthal.2019.10.004.
8. Qin B, Wang J, Yang Z. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74(11):1983–9.

9. Kabasakal Y, Kitapcioglu G, Turk T, Öder G, Durusoy R, Mete N. The prevalence of Sjögren's syndrome in adult women. *Scand J Rheumatol*. 2006;35(5):379–83. doi:10.1080/03009740600759704.
10. Priori R, Medda E, Conti F, Cassara EA, Sabbadini MG, Antonioli CM. Risk factors for Sjogren's syndrome: a case-control study. *Clin Exp Rheumatol*. 2007;25:378–84.
11. Yan T, Shen J, Chen J, Zhao M, Guo H, Wang Y. Differential expression of miR-17-92 cluster among varying histological stages of minor salivary gland in patients with primary Sjögren's syndrome. *Clin Exp Rheumatol*. 2019;37(3):49–54.
12. Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, Bosch X, Tzioufas AG. Topical and systemic medications for the treatment of primary Sjögren's syndrome. *Nat Rev Rheumatol*. 2012;8(7):399–411. doi:10.1038/nrrheum.2012.53.
13. Aqrawi LA, Chen X, Jensen JL, Morthen MK, Thiede B, Utheim Ø, et al. Severity of clinical dry eye manifestations influences protein expression in tear fluid of patients with primary Sjögren's syndrome. *PLoS One*. 2018;13:e0205762.
14. Akpek EK, Klimava A, Thorne JE, Martin D, Lekhanont K, Ostrovsky A. Evaluation of Patients With Dry Eye for Presence of Underlying Sjögren Syndrome. *Cornea*. 2009;28(5):493–7. doi:10.1097/ico.0b013e31818d3846.
15. Liew MS, Zhang M, Kim E. Prevalence and predictors of Sjogren's syndrome in a prospective cohort of patients with aqueous-deficient dry eye. *Br J Ophthalmol*. 2012;96:1498–1503.
16. Asbell PA, Maguire MG, Pistilli M. Omega-3 fatty acid supplementation for the treatment of dry eye disease. *N Engl J Med*. 2018;378:1681–90.
17. Castro F, Sanchez-Piedra M, Aandreu JL, Taboada VM, Olivé A, Rosas J, et al. Factors associated with severe dry eye in primary Sjögren's syndrome diagnosed patients. *Rheumatol Int*. 2018;38:1075–82.
18. Pinto A, Lindemeyer RG, Sollecito TP. Thalidomide in PFAPA syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol*. 2007;103:307. doi:10.1016/j.tripleo.2006.10.012.
19. Bayetto K, Logan RM. Sjögren's syndrome: a review of aetiology, pathogenesis, diagnosis and management. *Aust Dent J*. 2010;55:39–47. doi:10.1111/j.1834-7819.2010.01197.x.
20. Konttinen Y, Kasna-Ronkainen L. Sjögren's syndrome: viewpoint on pathogenesis. *Scand J Rheumatol*. 2002;116:15–22.
21. Coursey TG, Paiva CD. Managing Sjögren's Syndrome and non-Sjögren Syndrome dry eye with anti-inflammatory therapy. *Clin Ophthalmol*. 2014;8:1447–58.
22. Nikolov NP, Illei GG. Pathogenesis of Sjögren's syndrome. *Curr Opin Rheumatol*. 2009;21(5):465–70. doi:10.1097/bor.0b013e32832eba21.
23. Valtysdottir ST, Wide L, Hallgren R. Low serum dehydroepiandrosterone sulfate in women with primary Sjögren's syndrome as an isolated sign of impaired HPA axis function. *J Rheumatol*. 2001;28:1259–65.
24. Maurya RP, Singh VP, Chaudhary S, Roy M, Srivastav T. Prevalence of severe dry eye disease in postmenopausal women in North India: A teaching hospital study. *Indian J Obstet Gynecol Res*. 2019;6(1):94–6. doi:10.18231/2394-2754.2019.0021.
25. Lessard CJ, Li H, Adrianto I. Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjögren's syndrome. *Nat Genet*. 2013;45(11):1284–92.
26. Sandhya P, Kurien B, Danda D, Scofield R. Update on Pathogenesis of Sjogren's Syndrome. *Curr Rheumatol Rev*. 2017;13(1):5–22. doi:10.2174/1573397112666160714164149.
27. Nordmark G, Kristjansdottir G, Theander E, Appel S, Eriksson P, Vasaitis L, et al. Association of EBF1, FAM167A(C8orf13)-BLK and TNFSF4 gene variants with primary Sjögren's syndrome. *Genes Immun*. 2011;12(2):100–9. doi:10.1038/gene.2010.44.
28. Appel S, Hellard SL, Bruland O, Brun JG, Omdal R, Kristjansdottir G. Potential association of muscarinic receptor 3 gene variants with primary Sjogren's syndrome. *Anne Rheumatic Dis*. 2011;70(7):1327–9. doi:10.1136/ard.2010.138966.
29. Chen KS, Jiang MC, Li CJ, Liu OK, Tsai CSS. Discrimination between Sjögren's and Non-Sjögren's Sicca Syndrome by Sialoscintigraphy and Antibodies against α-Fodrin and Ro/La Autoantigens. *J Int Med Res*. 2009;37:1088–96. doi:10.1177/147323000903700413.
30. Liu KC, Huynh K, Grubbs J, Davis RM. Autoimmunity in the Pathogenesis and Treatment of Keratoconjunctivitis Sicca. *Curr Allergy Asthma Rep*. 2014;14(1). doi:10.1007/s11882-013-0403-7.
31. Mallery DL, McEwan WA, Bidgood SR, Towers GJ, Johnson CM, James LC. Antibodies mediate intracellular immunity through tripartite motif-containing 21 (TRIM21). *Proc Natl Acad Sci*. 2010;107(46):19985–90. doi:10.1073/pnas.1014074107.
32. Jauharoh SNA, Saegusa J, Sugimoto T, Ardianto B, Kasagi S, Sugiyama D, et al. SS-A/Ro52 promotes apoptosis by regulating Bcl-2 production. *Biochem Biophys Res Commun*. 2012;417(1):582–7. doi:10.1016/j.bbrc.2011.12.010.
33. Chen X, Smith JD, Shi H, Yang DD, Flavell RA, Wolin SL. The Ro Autoantigen Binds Misfolded U2 Small Nuclear RNAs and Assists Mammalian Cell Survival after UV Irradiation. *Curr Biol*. 2003;13(24):2206–11. doi:10.1016/j.cub.2003.11.028.
34. Liang C, Xiong K, Szulwach KE. Sjogren syndrome antigen B (SSB)/La promotes global microRNA expression by binding microRNA precursors through stem-loop recognition. *J Biol Chem*. 2013;288(1):723–36.
35. Liu Y, Tan H, Tian H, Liang C, Chen S, Liu Q. Autoantigen La promotes efficient RNAi, antiviral response, and transposon silencing by facilitating multiple-turnover RISC catalysis. *Mol Cell*. 2011;44(3):502–8.
36. Ogawa Y, Shimizu E, Tsubota K. Interferons and Dry Eye in Sjögren's Syndrome. *Int J Mol Sci*. 2018;19(11):3548. doi:10.3390/ijms19113548.
37. Hall JC, Baer AN, Shah AA, Criswell LA, Shiboski CH, Rosen A, et al. Molecular Subsetting of Interferon Pathways in Sjögren's Syndrome. *Arthritis Rheumatol*. 2015;67(9):2437–46. doi:10.1002/art.39204.
38. Bodewes ILA, Al-Ali S, Helden-Meeuwsen CG, Maria NI, Tarn J, Lendrem DW, et al. Systemic interferon type I and type II signatures in primary Sjögren's syndrome reveal differences in biological disease activity. *Rheumatology*. 2018;57(5):921–30. doi:10.1093/rheumatology/kex490.
39. Chodosh J, Dix RD, Howell WG. Staining characteristics and antiviral activity of sulforhodamine B and lissamine green B. *Invest Ophthalmol Vis Sci*. 1994;35:1046–58.
40. Reksten TR, Lessard CJ, Sivils KL. Genetics in Sjögren Syndrome. *Rheumatic Dis Clin North Am*. 2016;42(3):435–47. doi:10.1016/j.rdc.2016.03.003.
41. Jabs DA, Prendergast RA, Whittum-Hudson J. Cytokines in autoimmune lacrimal gland disease in MRL/MpJ mice. *Cornea*. 2000;19(Supplement 2):S97. doi:10.1097/00003226-200011002-00086.
42. Foulks GN, Forstot SL, Donshik PC, Forstot JZ, Goldstein MH, Lemp MA, et al. Clinical Guidelines for Management of Dry Eye Associated with Sjögren Disease. *Ocul Surf*. 2015;13(2):118–32. doi:10.1016/j.jtos.2014.12.001.
43. Bianciardi G, Latronico ME, Traversi C. Entropy of corneal nerve fibers distribution observed by laser scanning confocal microscopy: A noninvasive quantitative method to characterize the corneal innervation in Sjogren's syndrome patients. *Microsc Res Tech*. 2015;78(12):1069–74.
44. Villani E, Magnani F, Viola F, Santaniello A, Scorza R, Nucci P, et al. In Vivo Confocal Evaluation of the Ocular Surface Morpho-Functional Unit in Dry Eye. *Optom Vis Sci*. 2013;90(6):576–86. doi:10.1097/opx.0b013e318294c184.
45. Roszkowska AM, Oliverio GW, Aragona E, Inferrera L, Severo AA, Alessandrello F, et al. Ophthalmologic Manifestations of Primary Sjögren's Syndrome. *Genes*. 2021;12:365. doi:10.3390/genes12030365.
46. Stefanski AL, Tomiak C, Pleyer U, Dietrich T, Burmester GR, Dörner T. The Diagnosis and Treatment of Sjögren's Syndrome. *Dtsch Arztebl Int*. 2017;114:354–61. doi:10.3238/arztebl.2017.0354.

47. Akpek EK, Mathews P, Hahn S, Hessen M, Kim J, Grader-Beck T, et al. Ocular and Systemic Morbidity in a Longitudinal Cohort of Sjögren's Syndrome. *Ophthalmology*. 2015;122(1):56–61. doi:10.1016/j.ophtha.2014.07.026.
48. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol*. 1960;118:615–21.
49. Tashbayev B, Rusthen S, Young A, Herlofson BB, Hove LH, Singh PB, et al. Interdisciplinary, Comprehensive Oral and Ocular Evaluation of Patients with Primary Sjögren's Syndrome. *Sci Rep*. 2017;7:10761. doi:10.1038/s41598-017-10809-w.
50. Schaumberg DA, Gulati A, Mathers WD, Clinch T, Lemp MA, Nelson JD, et al. Development and Validation of a Short Global Dry Eye Symptom Index. *Ocul Surf*. 2007;5(1):50–7. doi:10.1016/s1542-0124(12)70053-8.
51. Chalmers RL, Begley CG, Caffery B. Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): Discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Cont Lens Anterior Eye*. 2010;33(2):55–60. doi:10.1016/j.clae.2009.12.010.
52. Whitcher JP, Shiboski CH, Shiboski SC, Heidenreich AM, Kitagawa K, Zhang S, et al. Sjögren's International Collaborative Clinical Alliance Research Groups. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. *Am J Ophthalmol*. 2010;149(3):405–15.
53. Sullivan BD, Whitmer D, Nichols KK, Tomlinson A, Foulks GN, Geerling G, et al. An Objective Approach to Dry Eye Disease Severity. *Invest Opthalmol Vis Sci*. 2010;51(12):6125–30. doi:10.1167/iovs.10-5390.
54. Lemp MA, Bron AJ, Baudouin C, Castillo JMB, Geffen D, Tauber J, et al. Tear Osmolarity in the Diagnosis and Management of Dry Eye Disease. *Am J Ophthalmol*. 2011;151(5):792–8. doi:10.1016/j.ajo.2010.10.032.
55. Sambursky R, Davitt WF, Latkany R, Tauber S, Starr C, Friedberg M, et al. Sensitivity and Specificity of a Point-of-Care Matrix Metalloproteinase 9 Immunoassay for Diagnosing Inflammation Related to Dry Eye. *JAMA Ophthalmol*. 2013;131(1):24–8. doi:10.1001/jamaophthalmol.2013.561.
56. Pflugfelder SC, Jones D, Ji Z, Afonso A, Monroy D. Altered cytokine balance in the tear fluid and conjunctiva of patients with Sjögren's syndrome keratoconjunctivitis sicca. *Curr Eye Res*. 1999;19(3):201–11. doi:10.1076/ceyr.19.3.201.5309.
57. Bron A, Abelson M, Ousler G. Methodologies to diagnose and monitor dry eye disease: report of the epidemiology subcommittee of the International Dry Eye Workshop. *Ocul Surf*. 2007;5(2):108–52.
58. Wolffsohn J, Arita R, Chalmers R. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15:539–74.
59. Acs M, Caffery B, Barnett M, Edmonds C, Johnson-Tong L, Maharaj R, et al. Customary practices in the monitoring of dry eye disease in Sjogren's syndrome. *J Optom*. 2018;11(4):232–41. doi:10.1016/j.optom.2018.05.001.
60. Rose-Nussbaumer J, Lietman TM, Shiboski CH, Shiboski S, Bunya VY, Akpek EK, et al. Inter-grader Agreement of the Ocular Staining Score in the Sjögren's International Clinical Collaborative Alliance (SICCA) Registry. 2015;160:1150–3.
61. Verstappen GM, van Nimwegen J, Vissink A, Kroese FGM, Bootsma H. The value of rituximab treatment in primary Sjögren's syndrome. *Clin Immunol*. 2017;182:62–71. doi:10.1016/j.clim.2017.05.002.
62. Feenstra RPG. What Is Actually Stained by Rose Bengal? *Arch Ophthalmol*. 1992;110(7):984–93. doi:10.1001/archopht.1992.01080190090035.
63. Bron AJ, Evans VE, Smith JA. Grading Of Corneal and Conjunctival Staining in the Context of Other Dry Eye Tests. *Cornea*. 2003;22(7):640–50. doi:10.1097/00003226-200310000-00008.
64. Feenstra RPG, Tseng SCG. Comparison of Fluorescein and Rose Bengal Staining. *Ophthalmology*. 1992;99(4):605–17. doi:10.1016/s0161-6420(92)31947-5.
65. Garcia DM, Oliveira FR, Módulo CM, Faustino J, Barbosa AP, Alves M, et al. Is Sjögren's syndrome dry eye similar to dry eye caused by other etiologies? Discriminating different diseases by dry eye tests. *PLOS ONE*. 2018;13(12):e0208420. doi:10.1371/journal.pone.0208420.
66. Chen X, Utheim Ø, Xiao J, Adil MY, Stojanovic A, Tashbayev B, et al. Meibomian gland features in a Norwegian cohort of patients with primary Sjögren´s syndrome. *PLOS ONE*. 2017;12(9):e0184284. doi:10.1371/journal.pone.0184284.
67. Zang S, Cui Y, Cui Y, Fei W. Meibomian gland dropout in Sjögren's syndrome and non-Sjögren's dry eye patients. *Eye*. 2018;32:1681–7. doi:10.1038/s41433-018-0149-5.
68. Palamar M, Ozsan N, Sahin F. Bilateral Lacrimal Gland Lymphoma in Sjögren Syndrome. *Case Rep Ophthalmol Med*. 2016;2016:1–3. doi:10.1155/2016/2798304.
69. Baldini C, Luciano N, Tarantini G, Pascale R, Sernissi F, Mosca M, et al. Salivary gland ultrasonography: a highly specific tool for the early diagnosis of primary Sjögren's syndrome. *Arthritis Res Ther*. 2015;17(1):146. doi:10.1186/s13075-015-0657-7.
70. Pepose JS, Akata RF, Pflugfelder SC, Voigt W. Mononuclear Cell Phenotypes and Immunoglobulin Gene Rearrangements in Lacrimal Gland Biopsies from Patients with Sjögren's Syndrome. *Ophthalmology*. 1990;97(12):1599–1605. doi:10.1016/s0161-6420(90)32372-2.
71. Hamm-Alvarez SF, Janga SR, Edman MC, Madrigal S, Shah M, Frousiakis SE, et al. Tear Cathepsin S as a Candidate Biomarker for Sjögren's Syndrome. *Arthritis Rheumatol*. 2014;66:1872–81. doi:10.1002/art.38633.
72. Bombardieri M, Argyropoulou OD, Ferro F, Coleby R, Pontarini E, Governato G, et al. One year in review 2020: pathogenesis of primary Sjögren's syndrome. *Clin Exp Rheumatol*. 2020;38(4):3–9.
73. Klinngam W, Janga SR, Lee C, Ju Y, Yarber F, Shah M, et al. Inhibition of Cathepsin S Reduces Lacrimal Gland Inflammation and Increases Tear Flow in a Mouse Model of Sjögren's Syndrome. *Sci Rep*. 2019;9(1):9559. doi:10.1038/s41598-019-45966-7.
74. Bunya VY, Ying GS, Maguire MG, Kuklinski E, Lin MC, Peskin E, et al. Prevalence of Novel Candidate Sjogren Syndrome Autoantibodies in the Dry Eye Assessment and Management (DREAM) Study. *Cornea*. 2018;37(11):1425–30. doi:10.1097/ico.0000000000001714.
75. Shen L, Suresh L, Lindemann M, Xuan J, Kowal P, Malyavantham K, et al. Novel autoantibodies in Sjogren's syndrome. *Clin Immunol*. 2012;145(3):251–5. doi:10.1016/j.clim.2012.09.013.
76. Meiners PM, Vissink A, Kroese FGM, Spijkervet FKL, Smitt-Kamminga NS, Abdulahad WH. Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). *Ann Rheumatic Dis*. 2014;73(7):1393–6. doi:10.1136/annrheumdis-2013-204653.
77. Meijer JM, Meiners PM, Vissink A, Spijkervet FK, Abdulahad W, Kamminga N, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: A randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatism*. 2010;62(4):960–8. doi:10.1002/art.27314.
78. Pijpe J, Imhoff GW, Spijkervet FKL, Roodenburg JLN, Wolbink GJ, Mansour K, et al. Rituximab treatment in patients with primary Sjögren's syndrome: An open-label phase II study. *Arthritis Rheumatism*. 2005;52(9):2740–50. doi:10.1002/art.21260.
79. Vitali C. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheumatic Dis*. 2002;61(6):554–8. doi:10.1136/ard.61.6.554.
80. Kim M, Kim HS, Na KS. Correlation between Tear Osmolarity and Other Ocular Surface Parameters in Primary Sjögren's Syndrome. *Korean J Ophthalmol*. 2017;31(1):25–31.
81. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis*. 2016;76:9–16.

82. Samarkos M, Moutsopoulos HM. Recent advances in the management of ocular complications of sjögren's syndrome. *Curr Allergy Asthma Rep*. 2005;5(4):327–32. doi:10.1007/s11882-005-0077-x.
83. Mavragani CP, Moutsopoulos NM, Moutsopoulos HM. The management of Sjögren's syndrome. *Nat Clin Pract Rheumatol*. 2006;2(5):252–61. doi:10.1038/ncprheum0165.
84. Ciurtin C, Ostas A, Cojocaru VM, Walsh SB, Isenberg DA. Advances in the treatment of ocular dryness associated with Sjögren′s syndrome. *Semin Arthritis Rheumatism*. 2015;45(3):321–7. doi:10.1016/j.semarthrit.2015.06.007.
85. Passi S, Pierson K, Kamalani H, Santiago-Caban L, Muthappan VV, Moshirfar M. Artificial tears potpourri: a literature review. *Clin Ophthalmol*. 2014;8:1419–33. doi:10.2147/opth.s65263.
86. Luchs JI, Nelinson DS, Macy JI. Group LaCS Efficacy of hydroxypropyl cellulose ophthalmic inserts (LACRISERT) in subsets of patients with dry eye syndrome: findings from a patient registry. *Cornea*. 2010;29:1417–27.
87. Jones L, Downie LE, Benitez-Del-Castillo JM, Dana R, Deng SX, Dong P, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017;15:575–28.
88. Vehof J, Utheim TP, Bootsma H, Hammond CJ. Advances, limitations and future perspectives in the diagnosis and management of dry eye in Sjögren's syndrome. *Clin Exp Rheumatol*. 2020;38(4):301–9.
89. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. *Immunopharmacology*. 2000;47(2-3):119–25.
90. Brignole F, Pisella PJ, Jean MS, Goldschild M, Goguel A, Baudouin C. Flow cytometric analysis of inflammatory markers in KCS: 6-month treatment with topical cyclosporin A. *Invest Ophthalmol Vis Sci*. 2001;42(1):90–5.
91. Kunert KS. Analysis of Topical Cyclosporine Treatment of Patients With Dry Eye Syndrome<subtitle>Effect on Conjunctival Lymphocytes</subtitle>. *Arch Ophthalmol*. 2000;118(11):1489–96. doi:10.1001/archopht.118.11.1489.
92. Pflugfelder SC, Solomon A, Stern ME. The Diagnosis and Management of Dry Eye. *Cornea*. 2000;19(5):644–9. doi:10.1097/00003226-200009000-00009.
93. Rosenberg ES, Asbell PA. Essential Fatty Acids in the Treatment of Dry Eye. *Ocul Surf*. 2010;8(1):18–28. doi:10.1016/s1542-0124(12)70214-8.
94. Holland EJ, Whitley WO, Sall K, Lane SS, Raychaudhuri A, Zhang SY, et al. Lifitegrast clinical efficacy for treatment of signs and symptoms of dry eye disease across three randomized controlled trials. *Curr Med Res Opin*. 2016;32(10):1759–65. doi:10.1080/03007995.2016.1210107.
95. Gm K. Lifitegrast ophthalmic solution 5%: a review in dry eye disease. *Drugs*. 2017;77:201–209.
96. Holland E, Luchs J, Karpecki PM. Lifitegrast for the treatment of dry eye disease: results of a Phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3). *Ophthalmology*. 2017;124:5360.
97. Nichols KK, Donnenfeld ED, Karpecki PM, Hovanesian JA, Raychaudhuri A, Shojaei A, et al. Safety and tolerability of lifitegrast ophthalmic solution 5.0%: Pooled analysis of five randomized controlled trials in dry eye disease. *Eur J Ophthalmol*. 2019;29(4):394–401. doi:10.1177/1120672118791936.
98. Vivino FB. Pilocarpine Tablets for the Treatment of Dry Mouth and Dry Eye Symptoms in Patients With Sjögren Syndrome<subtitle>A Randomized, Placebo-Controlled, Fixed-Dose, Multicenter Trial</subtitle>. *Arch Intern Med*. 1999;159(2):174–81. doi:10.1001/archinte.159.2.174.
99. Tsifetaki N. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjogren's syndrome: a randomised 12 week controlled study. *Ann Rheumatic Dis*. 2003;62(12):1204–7. doi:10.1136/ard.2002.003889.
100. Arimoto A, Kitagawa K, Mita N, Takahashi Y, Shibuya E, Sasaki H. Effect of Rebamipide Ophthalmic Suspension on Signs and Symptoms of Keratoconjunctivitis Sicca in Sjögren Syndrome Patients With or Without Punctal Occlusions. *Cornea*. 2014;33(8):806–11. doi:10.1097/ico.0000000000000155.
101. Dorennavar L, Maurya RP, Singh VP, Singh MK, Sharma K, Sharma R. The role of Rebamipide ophthalmic suspension in management of dry eye disease. *Indian J Clin Exp Ophthalmol*. 2015;1(4):191–6. doi:10.5958/2395-1451.2015.00025.6.
102. Jeon HS, Hyon JY. The Efficacy of Diquafosol Ophthalmic Solution in Non-Sjögren and Sjögren Syndrome Dry Eye Patients Unresponsive to Artificial Tear. *J Ocul Pharmacol Ther*. 2016;32(7):463–8. doi:10.1089/jop.2015.0081.
103. Tauber J, Davitt WF, Bokosky JE, Nichols KK, Yerxa BR, Schaberg AE, et al. Double-Masked, Placebo-Controlled Safety and Efficacy Trial of Diquafosol Tetrasodium (INS365) Ophthalmic Solution for the Treatment of Dry Eye. *Cornea*. 2004;23(8):784–92. doi:10.1097/01.ico.0000133993.14768.a9.
104. Bremond-Gignac D, Gicquel JJ, Chiambaretta F. Pharmacokinetic evaluation of diquafosol tetrasodium for the treatment of Sjögren's syndrome. *Expert Opin Drug Metab Toxicol*. 2014;10(6):905–13. doi:10.1517/17425255.2014.915026.
105. Chao W, Belmonte C, Benitez D, Castillo JM. Report of the Inaugural Meeting of the TFOS i(2) = initiating innovation series: targeting the unmet need for dry eye treatment. *Ocul Surf*. 2016;14:264–16.
106. Sakamoto A, Kitagawa K, Tatami A. Efficacy and Retention Rate of Two Types of Silicone Punctal Plugs in Patients With and Without Sj??gren Syndrome. *Cornea*. 2004;23(3):249–54. doi:10.1097/00003226-200404000-00006.
107. Tai MC, Cosar CB, Cohen EJ, Rapuano CJ, Laibson PR. The Clinical Efficacy of Silicone Punctal Plug Therapy. *Cornea*. 2002;21(2):135–9. doi:10.1097/00003226-200203000-00001.
108. Liu L, Hartwig D, Harloff S, Herminghaus P, Wedel T, Geerling G. An optimised protocol for the production of autologous serum eyedrops. *Graefes Arch Clin Exp Ophthalmol*. 2005;243(7):706–14. doi:10.1007/s00417-004-1106-5.
109. Kojima T, Ishida R, Dogru M, Goto E, Matsumoto Y, Kaido M, et al. The effect of autologous serum eyedrops in the treatment of severe dry eye disease: A prospective randomized case-control study. *Am J Ophthalmol*. 2005;139(2):242–6. doi:10.1016/j.ajo.2004.08.040.
110. Nepp J, Knoetzl W, Prinz A, Hoeller S, Prinz M. Management of moderate-to-severe dry eye disease using chitosan-N-acetylcysteine (Lacrimera®) eye drops: a retrospective case series. *Int Ophthalmol*. 2020;40(6):1547–52. doi:10.1007/s10792-020-01324-5.
111. Schmidl D, Werkmeister R, Kaya S, Unterhuber A, Witkowska KJ, Baumgartner R, et al. A Controlled, Randomized Double-Blind Study to Evaluate the Safety and Efficacy of Chitosan-N-Acetylcysteine for the Treatment of Dry Eye Syndrome. *J Ocul Pharmacol Ther*. 2017;33(5):375–82. doi:10.1089/jop.2016.0123.
112. Lambiase A, Sullivan BD, Schmidt TA, Sullivan DA, Jay GD, Truitt ER, et al. A Two-Week, Randomized, Double-masked Study to Evaluate Safety and Efficacy of Lubricin (150 μg/mL) Eye Drops Versus Sodium Hyaluronate (HA) 0.18% Eye Drops (Vismed®) in Patients with Moderate Dry Eye Disease. *Ocul Surf*. 2017;15(1):77–87.
113. Russo PA, Bouchard CS, Galasso JM. Extended-Wear Silicone Hydrogel Soft Contact Lenses in the Management of Moderate to Severe Dry Eye Signs and Symptoms Secondary to Graft-Versus-Host Disease. *Eye Contact Lens*. 2007;33(3):144–7. doi:10.1097/01.icl.0000244154.76214.2d.
114. Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment of meibomian gland dysfunction. *Adv Exp Med Biol*. 1994;350:293–8.
115. Lane SS, DuBiner HB, Epstein RJ, Ernest PH, Greiner JV, Hardten DR, et al. A New System, the LipiFlow, for the Treatment of Meibomian Gland Dysfunction. *Cornea*. 2012;31(4):396–404. doi:10.1097/ico.0b013e318239aaea.
116. Finis D, Hayajneh J, König C, Borrelli M, Schrader S, Geerling G. Evaluation of an Automated Thermodynamic Treatment (LipiFlow®) System for Meibomian Gland Dysfunction: A Prospective, Randomized, Observer-Masked Trial. *Ocul Surf*.

2014;12(2):146–54. doi:10.1016/j.jtos.2013.12.001.
117. Benvenuti D. Botox use in prevention of dry eyes. *Plast Reconstr Surg*. 1998;102:918.

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