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# Sjögren's Syndrome as an Ocular Problem: Signs and Symptoms, Diagnosis, Treatment

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## Abstract

Sjögren's syndrome (SS) is an autoimmune disease of exocrine glands, which is characterized by dry mouth and dry eye, though ocular disturbances, such as dry eye disease, may be the first sign of the problem. In pathogenesis of SS, activated T-cells and B-cells infiltrate the lacrimal glands and autoimmune process leading to cell destruction. This process causes hyposalivation and aqueous-deficient dry eye disease. Evaporative dry eye disease is connected with Meibomian gland dysfunction (MGD) and/or goblet cell loss. There are many questionnaires and tests to dry eye disease diagnosing, but there is no "gold standard." Correlation of data from symptom questionnaires and results of ocular staining score, Schirmer test I (without anesthesia), and break-up-time make it easier to diagnose. The treatment of SS includes both local (tear drops and moistures) and systemic (nonsteroidal anti-inflammatory drugs—NSAIDs, glucocorticoids, and disease-modifying anti-rheumatic drugs—biologics) therapies, but it is individual. We would like to present recent data on the ocular involvement and perspective of dry eye disease diagnosis and treatment in patients with SS.

**Keywords:** dry eye, Sjögren's syndrome, pathogenesis, diagnostic tests and questionnaires, topical therapy, immunomodulatory therapy

## 1. Introduction

Sjögren's syndrome (SS) is a rheumatic autoimmune disease in which exocrine glands (salivary and lacrimal glands) are involved that results in clinical symptoms of dry mouth and dry eye. For the first time, SS-like clinical condition was described by Mikulicz in 1892 [1]. However, the disease was fully described (clinically and histopathology) later by the Swedish ophthalmologist Henrik Sjögren in 1930. He detected coincidence of rheumatism and hyposalivation of lacrimal and salivary glands and introduced the new term *keratoconjunctivitis sicca* to describe significant conjunctival and corneal staining with both dyes: methylene blue and rose bengal [1–3]. He also compared keratoconjunctivitis sicca and xerophthalmia seen in vitamin A deficiency and postulated that these cases represented a systemic disease. His doctoral thesis on this problem did not receive recognition and the author was disqualified from receiving PhD. Though his academic career was over, he lived on the day when the disease was named after him [2].

SS affects the exocrine glands; lymphocytic infiltration leads to sicca syndrome of the eyes, oral cavity, pharynx, larynx, and/or vagina [1, 3–6]. Systemic manifestations of SS are divided into visceral (lung, heart, kidney, endocrine, nervous system, gastrointestinal) and non-visceral (skin, myalgia, arthralgia). The risk of lymphoma is higher in patients with SS than in general population [1, 4, 6–8]. SS can be primary-pSS (without any other accompanying symptoms) or secondary-sSS (with other autoimmune diseases: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polyarteritis nodosa, systemic sclerosis, granulomatosis with polyangiitis (GPA), primary biliary cholangitis (PBC), mixed connective tissue disease, occult thyroid eye disease) [1, 3–6, 9–11].

Dry eye disease (DED) problems are involved in diagnostic criteria of SS as an important part of diagnosis. Patients with DED seek medical help for many years prior to SS diagnosis—about 25% of DED patients have an underlying rheumatic condition, commonly pSS. Only one-third of patients with SS carried final diagnosis prior to ocular symptoms [1, 11, 12]. Some studies demonstrated coincidence of DED and SS in 46.7% cases [1, 11].

## **2. Pathophysiology**

Primary Sjögren's syndrome is a multifactorial disorder including genetic predisposition, hormonal, and environmental factors [6, 13]. The pathogenesis of SS is incompletely understood. For years, it has been considered as T-cell dependent autoimmune response; now, the role of B cells is also described and is known as important. Tissue destruction is associated with the infiltration by both activated T and autoreactive B cells [1, 4, 6].

Plasmacytoid dendritic cells produce interferon (IFN)-I responsible for apoptosis/necrosis of glandular epithelial cells—it upregulates the major histocompatibility complex (MHC) molecules (class I and II) and costimulatory molecules (CD80,CD86), promotes production of cytokines (interleukin IL-6, IL-10, IL-12, IL-15, IF- $\gamma$ , tissue growth factor TGF- $\beta$ , tumor necrosis factor TNF- $\alpha$ ), and chemokines (CXCL-11, CXCL-12, CXCL-13, CXCL-21) responsible for leukocytes migration resulting activation of the inflammatory reaction [1, 4, 6, 14, 15].

Glandular epithelial cells' necrosis/apoptosis reveals Sjögren-specific antibodies A (SSA, anti-RO) and B (SSB, anti-La)—though the role of these autoantigens is not completely clear, but the presence of them is one of the diagnostic criteria of pSS [1, 4]. Moreover, the presence of macrophage-derived chemokine (MDC) and thymus-activation-regulated chemokine (TARC), abnormal distribution of aquaporin (AQP)-5 cell membrane transporter, and defect in AQP-5 trafficking increased B-cell-activating factor (BAFF) and the matrix metalloproteinases (MMP) level were described in relationship with tissue damage in pSS [1, 4, 15–17].

Autoantibodies against type-3 muscarinic acetylcholine receptors are the suggested reason of peripheral neuropathies (PN) associated with SS though it has not been proved yet [6, 18].

## **3. Classification criteria**

To standardize the diagnosis in patients taking part in clinical studies, to analyze results, and to facilitate the comparison of patients between centers, the classification criteria should be established.

In 1993, the Preliminary European Classification criteria for SS were published, and for almost 10 years have been the base for clinical, observational, and interventional studies [6, 19]. In 2002, the American-European Consensus Group (AECG) published a revised version of the SS classification criteria [6, 20–22]. All documents include ocular disturbances. AECG criteria for DED consist of symptoms and signs. Positive response to one question: (1) Have you had daily, persistent, troublesome dry eyes for >3 months? (2) Do you have a recurrent sensation of sand or gravel in the eyes? (3) Do you use tear substitutes >3 times a day? or positive one of tests: Schirmer without anesthesia  $\leq 5$  mm/5 min or vital dye staining of the ocular surface ( $\geq 4$  van Bijsterveld or Ocular Staining Score OSS  $\geq 5$ , [19–23]).

Because of their restrictive nature, the American College of Rheumatology approved the Sjögren's International Collaborative Clinical Alliance (SICCA) approach in 2012. To diagnose SS with ACR/SICCA criteria at least 2 of 3 are necessary: (1) a positive serum anti-Ro/-SSA or/and anti-La/SSB or [positive rheumatoid factor RF and antinuclear antibody (ANA)  $\geq 1:320$ ], (2) focal lymphocytic sialadenitis defined as focus score  $\geq 1$  focus/4 mm<sup>2</sup> in labial salivary gland biopsy samples, (3) OSS  $\geq 3$  [6, 21, 23].

Main differences between ACR/SICCA and AECG criteria are: (1) no subjective ocular and buccal symptoms and morphological or functional tests for salivary glands, (2) new OSS proposed by SICCA as the only test for ocular problems, (3) the association of RF positivity and ANA titer 1:320 as equivalent to anti-SSA/-SSB positivity [6, 21].

In 2016, ACR and EULAR published new pSS criteria containing again the Schirmer test and OSS in the dry eye assessment, as well as the test of unstimulated saliva production as a measuring tool for dryness in the mouth. The assessment of minor salivary gland biopsies and confirmation of the presence of the SS-A/Ro antibody were of particular importance. The remaining autoantibodies were not considered to be peculiar enough to diagnose pSS [21].

#### **4. Ocular manifestation of SS**

The main ocular manifestation of SS is DED. It is mainly a result of impaired lacrimal gland function due to inflammatory tissue damage. Hyposecretion of tears leads to aqueous-deficient DED. Moreover, exocrine glands of conjunctiva are also affected in SS and in connection with goblet cells reduction reveal evaporative DED [1, 6, 9, 22]. Ocular surface inflammation with conjunctival hyperemia and corneal epithelial damage leads to functional vision impairment [1, 2, 6, 22, 24]. Squamous metaplasia of the ocular surface epithelium, follicular conjunctivitis, corneal epitheliopathy, filamentary keratitis, sterile infiltrates, scleritis, poor epithelial integrity, recurrent erosions, dysesthesia, corneal ulceration, vascularization, opacification, and sometimes perforation were also described in SS patients [1, 2, 6, 22, 25].

#### **5. Diagnostic procedures for DED**

Dry eye disease among other diseases is the symptom causing the greatest morbidity and impairment of quality of life. Therefore, the patient is actively seeking a medical help. DED is typically diagnosed by evaluation of both eye symptoms and results of eye examination that symptoms not always match signs. Some patients have no symptoms though they have changes of ocular surface and others have significant eye discomfort, but there are very little signs in eye examination [1, 2, 22, 26–28].



## 5.1 Symptoms

Three characteristic features define DED: symptoms of discomfort, visual disturbance, and tear film instability with potential damage of ocular surface [9, 22, 28]. The discomfort is described as itching, stinging, burning, “foreign body sensation,” or, occasionally pain. Visual disturbance means fluctuation of vision, especially during reading or working at a computer. In those cases, blinking recovers the vision [22, 28].

There are several questionnaires for the assessment of DED symptoms: Ocular Surface Disease Index (OSDI), the McMonnies questionnaire, the Impact of Dry Eye on Everyday Life survey (IDEEL), the Symptom Assessment in Dry Eye survey (SANDE), and the Standard Patient Evaluation of Eye Dryness questionnaire (SPEED). They are used as screening tests for DED, to diagnose DED, to monitor changes over time, and to control effect of the therapy in both clinical practice and research [6, 22, 23, 28]. Schaumberg et al. proposed a short questionnaire for clinical DED screening. It consists of only three questions: (1) Have you ever been diagnosed by a clinician as having dry eye syndrome? (2) How often do your eyes feel dry/not wet enough? and (3) How often do your eyes feel irritated? [28–30]. It has turned out that 2 specific symptoms queried (dryness and irritation) are equivalent to asking up to 16 symptom questions [28, 31].

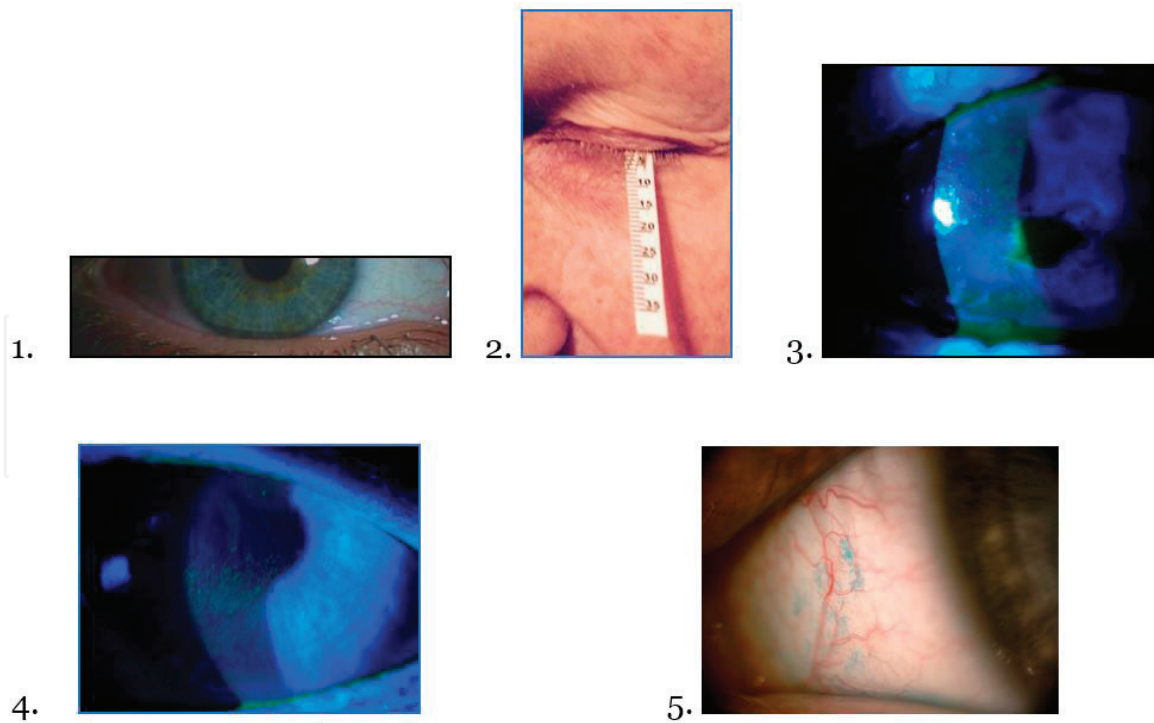
## 5.2 Signs

Evaluation of DED considers on: tear function, tear composition, and ocular surface changes.

The biomicroscopic examination evaluates luster and integrity of the tear film, the marginal tear strip, debris, and inflammatory cells in the tear film. The marginal tear strip is normally 1 mm in height and in DED is reduced. In clinical practice, a tear meniscus below 0.2 mm is regarded as pathological [2, 6, 9, 22, 25, 28, 32]. It is observed with the wide beam of the light and measured with narrow beam or optical instruments (description of those instruments and the interpretation of their measurements are available on the Tear Film and Ocular Surface Society website; [www.tearfilm.org](http://www.tearfilm.org)) [9, 28]. Corneal filaments are responsible for uncomfortable or painful sensation of patients [28] **Figure 1—(1)**.

Tear film instability is produced by either aqueous-deficient or evaporative or a combination of both mechanisms of DED. It can be also effect of ocular surface irregularities. To determine tear film stability tear film break-up time (TBUT) is used. The fluorescein dye is placed into the tear film and slit lamp with cobalt blue filtered light examination is performed: breakup is determined by a dark spot forming in the tear film. Normal BUT is greater than 10 s [2, 6, 9, 22, 28]. Devices using computer-analyzed reflections from the cornea has also been used for noninvasive tear stability analysis (noninvasive tear film break-up time NITBUT) [9, 28, 32–34] **Figure 1—(3)**.

The Schirmer test is described as “test to measure change in tear volume (production)” [9, 22]. A small strip of filter paper (5 × 35 mm) is placed on the margin of lower eyelid at the junction of the lateral and middle third of the lid. After 5 min, wetting of the strip is measured. If the test is performed without anesthesia-reflex tearing (e.g., tearing in response to a stimulus), the cutoff value is 5 mm; if the test is done after topical anesthesia-nonreflex (basal tears), the cutoff value is 3 mm [2, 6, 9, 22, 25, 28]. Although inter- and intraindividual differences were described, the range and absolute values are reduced in aqueous-deficient dry eye [7, 32]. Some clinicians use the phenol red thread test to measure tear volume; a small thread impregnated with phenol red dye is placed on the lower lid margin for 15 s. The normal value of the thread wetting is over 10 mm [9, 28, 32], **Figure 1—(2)**.



**Figure 1.**  
*Common diagnostic tests for dry eye disease: (1) tear film meniscus; (2) Schirmer test; (3) fluorescein break-up time; (4) fluorescein staining; and (5) lissamine green staining.*

The tear film composition analysis includes measurements of tear osmolarity (TO) and levels of inflammatory mediators. Elevated osmolarity of the tear film is a characteristic for DED though there is no suggested cutoff value for SS-related DED and further investigations should be conducted to establish it [9, 28, 32, 35, 36]. There is positive correlation between TO and OSDI score and OSS and negative correlation between osmolarity and Schirmer I test [28, 37]. Some studies found that a higher TO was associated with lower OSDI score in SS patients that was connected with the less corneal sensitivity [35, 38, 39]. TO measurements of both eyes are recommended: in early stages of DED, transient lower TO was noted; the effect was asymmetrical and this effect was not seen in subject without DED [28].

Measurements of inflammatory mediators in the tear film help to identify the inflammatory reaction and the severity of DED [22, 28, 38]. The levels of various cytokines (TNF- $\alpha$ , IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-10, IL-12P70, IL-13, MIP-1 $\alpha$ , IFN- $\gamma$ ) and MMP-9 in tears of DED patients are significantly higher than those in normal people [22, 28, 40, 41]. Statistical differences among subclasses of DED for IL-8 and TNF- $\alpha$  were observed and it could be significant for diagnosing and treatment of DED [40]. The activity of cathepsin S (CTSS) in tears and the level of HLA-Dr in impression cytology were higher in patients with SS than in patients with non-SS DED and healthy subjects [22].

Ocular surface evaluation is commonly clinically performed with the instillation of topical dyes. Fluorescein and lissamine green (or rose bengal) are vital dyes used to determine the integrity of the cornea and conjunctiva. Fluorescein is used for corneal examination (it stains punctate erosions), lissamine green (or rose Bengal) for conjunctival staining (both dyes stain mucus strands, filaments, and areas of epithelium unprotected by normal glycocalyx) [2, 6, 9, 22, 28]. Staining indicates corneal surface disease: greater staining means greater severity of DED. Conjunctival staining usually occurs before corneal staining, medial before temporal conjunctival staining [9, 28]. To evaluate and grade staining there are several systems such as 1995 NEI/industry Workshop System, the Oxford System, the van Bijsterveld system, the Ocular Staining Score (OSS) developed by SICCA [9, 22, 25, 28, 32] **Figure 1—(4, 5).**

Meibomian gland dysfunction (MGD) is defined as: “a chronic, diffuse abnormality of the Meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion; this may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease” [22, 41, 42]. MGD is the common cause of evaporative DED. Studies of SS patients found that MGD is common problem of them; they have higher Meibomian gland dropout scores compared with healthy group and worse Meibomian gland expressibility compared to non-SS DED patients [22, 24, 43]. The lipid layer is an important factor for ocular surface health and tear film stability [22, 44]. The thickness of this layer (lipid layer thickness LLT) is changed in DED and MGD; healthy subjects have LLT thinner than DED [22, 24, 45–47].

Imaging of the ocular surface is a valuable tool to document and determine changes, as well as differentiate aqueous-deficient and evaporative DED. New devices perform minimally invasive objective measurements (no drops, no touching of the eye) of NITBUT, TMH, images of the Meibomian glands (meibography), bulbar redness, and LLT [9, 22, 47–50].

An *in vivo* confocal study demonstrated morphologic changes in corneas of SS patients: a decrease in central corneal thickness was hypothesized to be due to inflammatory process, a reduced number of subbasal plexus fibers may explain the phenomenon of decreased corneal sensitivity [51, 52].

## **6. Treatment of SS-related DED**

Dry eye from SS is more severe than idiopathic one, so effective in idiopathic DED treatment may or may not work in SS. After diagnosing SS, the aim of the treatment is to maintain the tear film integrity through preservation, augmentation, and/or replacement of the deficient tear secretion [28, 51, 52]. There are many different therapies for DED, but there is no one treatment that works for everybody [22, 28, 32, 53, 54]. Though management approach of DED has changed over the years, some principles persist [28, 32, 54]. The treatment strategy is based upon the severity of DED and patients response to each added therapy. It includes patients' education, tears supplementation, management of MGD, inflammation of the ocular surface, and/or associated systemic disease [28, 32, 54].

### **6.1 Patient education**

Good cooperation of the DED patient requires understanding by them the disease (chronic), the aggravating factors (e.g., cigarette smoke, dry heating air, air conditioning, low humidity, pollutions, systemic medications that reduce tear secretion), and the management strategy (long-term and possibly slow to take effect). Some modifications of environment and activities of daily living can improve patients' quality of life [28, 32, 54, 55].

### **6.2 Tear supplementation: artificial tears**

Artificial tears are a standard of therapy for all severity grades of DED. The aim of this therapy in SS is to add tear film volume, to increase time of tear supplement on ocular surface and to reduce friction between lid and globe [28].

These preparations are not similar to natural tears: the main ingredients of them are lubricants or viscosity agents. Tear supplements varied in formulas: some of them include electrolytes, which are in normal tears to prevent ocular surface damage, some of them are hypotonic or distribute between the tear film and intracellular



fluid to protect against the pro-inflammatory effect of tears hyperosmolarity. They are based on polyvinyl alcohol, povidone, hydroxypropyl guar, cellulose derivatives, and hyaluronic acid. To mimic lipid component of tears triglycerides, phospholipids, and castor oil are used. Depending on viscosity of the lubricant (macromolecular complexes that increase the residence time of the supplement in the tear film) and thickness of supplement they may cause blurred vision; gels are more viscous than solutions, ophthalmic ointments are the thickest of lubrications. Typically, ointments are used before bedtime to provide DED symptoms, enabling sleep [28, 32, 54, 56, 57].

Preservatives (benzalkonium chloride or EDTA) in the tear supplements are potentially toxic to the ocular surface (epitheliotoxic). The toxicity of them increases in patients with DED because of frequent use of drops and decreased tears volume. The usage of artificial tears more than 4–6 times a day requires preservative-free unit dose vials [28, 54, 58].

There is wide variety of tear supplements but none is clearly superior. “The main variables in the formulation of ocular lubricants regard the concentration of and choice of electrolytes, the osmolarity and the type of viscosity/polymeric system, the presence or absence of preservative, and, if present, the type of preservative” [28, 54].

Long-acting ocular surface lubrication is also achievable through the hydroxypropyl cellulose insert usage. The insert is placed in the inferior conjunctival fornix and dissolves at body temperature. Thickening the tear film it decreases the need for frequent topical lubrication, used at bedtime it substitutes the ointment [28, 54, 59].

### **6.3 Anti-inflammatory therapy**

Since inflammation plays a key role in the pathogenesis of DED, many anti-inflammatory therapies have been evaluated in clinical trials and animal models. Better control of inflammatory reaction means DED symptoms and signs improvement.

#### *6.3.1 Topical corticosteroids*

There are some studies on short-term topical use of steroids in patients with SS and DED [9, 22, 28, 54, 60]. A 2- to 4-week course of treatment in patients with moderate to severe DED showed an improvement in both symptoms and signs: decreased symptom score, conjunctival hyperemia and corneal fluorescein staining, better TFBUT and Schirmer test measurements, higher numbers of goblet cells on impression cytology and lower numbers of inflammatory cells [28, 52, 60–63]. Topical steroids as a pulse therapy was noted as safe and effective one [60]. There are possible complications associated with long-term steroids usage: cataract, glaucoma, and infections. Elevated intraocular pressure and posterior subcapsular cataracts were described in patients using steroids over 3 months [28, 64].

#### *6.3.2 Topical cyclosporine A*

Cyclosporine A (CsA) is one of the powerful anti-T-cell immunosuppressive agents, but with no bone marrow suppression. The mechanism of action includes both inhibition of T-lymphocyte activation and other inhibitory properties, as the ability to inhibit apoptosis of other cells [28, 54, 65, 66]. Topical CsA reduce the cell-mediated inflammatory reactions [66] that results in improvement in symptoms (blurred vision, ocular dryness, foreign body sensation, and epiphora), reduction of fluorescein staining, better tear production (Schirmer test), reduction of pro-inflammatory cytokine and HLA-DR expression, increase of goblet cell density [2, 22, 28, 32, 67, 68]. Better tears production is probably connected with local release of parasympathetic neurotransmitters [32, 69]. CsA instilled to the conjunctival



sac seems to be the first therapeutic (not only symptomatic as others) treatment for patients with moderate to severe DED due to aqueous deficiency [66, 70].

The use of topical CsA for evaporative DED due to MGD is recommended by the International Tear Film and Ocular Surface Workshop on Meibomian Gland Dysfunction [28, 54, 71]. Traditional treatment of posterior blepharitis and MGD include lid hygiene, massages, hot compresses, low-dose tetracyclines, and topical antibiotics [28, 32, 71]. In some studies, the CsA-treated patients had a greater decrease in the number of obstructed Meibomian gland, improvement in the viscosity of Meibomian gland secretion, TFBUT, staining scores, and Schirmer scores than those treated in traditional way [28, 72, 73].

Long-term study confirmed safety of topical cyclosporine in 3-year follow-up [28, 74].

### *6.3.3 Topical lifitegrast*

Lifitegrast is a direct competitive antagonist of binding of lymphocyte function-associated antigen 1 (LFA-1) to intracellular adhesion molecule 1 (ICAM-1). Interaction between LFA-1 and ICAM-1 leads to T-lymphocyte adhesion to endothelial cells, migration to tissue, antigen presentation and recognition facilitating the formation of an immunological synapse. It releases inflammatory mediators, cytokines, chemokines, TNF- $\alpha$ , and IL-1 which are responsible for perpetuation and intensification DED inflammation [2, 22, 75–79]. The clinical efficacy of lifitegrast in patients with DED has been reported: improvement in symptom scores and ocular staining score in patients using it for 12 weeks. No serious ocular adverse events occurred [22, 75–79]. However, there are no studies comparing lifitegrast and other anti-inflammatory agents, evaluating whether lifitegrast in combination therapy could work better in DED—those problems need further studies [79].

## **6.4 Biological tear substitutes**

### *6.4.1 Autologous serum*

Serum is the fluid component of full blood that remains after clotting [54]. Human serum is similar to natural tears and contains many important components as: (1) epithelial growth factor EGF (acceleration of epithelial cell migration and anti-apoptotic effects); (2) transforming growth factor- $\beta$ /TGF- $\beta$  (involved in the epithelial and stromal repair process); (3) vitamin A (prevent epithelial squamous metaplasia and modulate the expression of thrombospondin-1); (4) thrombospondin-2, vascular endothelial growth factor A/VEGF-A, metallopeptidase-9 which with TGF- $\beta$  promote wound healing; (5) albumin (anti-apoptotic activity); (6)  $\alpha$ -2 macroglobulin (exhibits anti-collagenase activity); (7) fibronectin (involved in cell migration); (8) substance P and insulin-like growth factor (potential role in corneal epithelial migration and adhesion); and (9) immunoglobulins and lysozyme (bactericidal and bacteriostatic effect). Significant improvement in symptoms, fluorescein TFBUT, and ocular surface staining score were reported after autologous serum drops treatment [28, 54, 80–82]. However, some studies reported no significant advantage in tear film stability, Schirmer test, or fluorescein staining in the use of AS over AF [83–85]. It is free of preservatives and has osmolarity and biomechanical properties similar to natural tears [54, 80, 84].

### *6.4.2 Autologous plasma*

Plasma rich in growth factors (PRGF) and platelet-rich plasma (PRP) have been reported as successful treatment in DED patients [54, 84, 85]. Both of them (PRGF and PRP) are liberated from the platelets during preparation. Those components

help in the proliferation, migration, and differentiation of corneal epithelial cells [84–87]. Both PRGF and PRP are preservative-free, well tolerated with almost no side effects [84–87]. Further investigations to compare them with other hemoderivatives and with commercial artificial tear eye drops are necessary.

## **6.5 Tear stimulation: secretagogues**

“A secretagogue is a substance that causes another substance to be secreted” [28, 54]. Oral pilocarpine and cevimeline are indicated for treatment of dryness in SS. As muscarinic agonists, they stimulate secretion of saliva, aqueous tear from lacrimal glands, conjunctival epithelium, and mucin from goblet cells [52]. Some studies have shown their effectiveness in DED treatment in SS patients. The oral 10–30 mg/day of pilocarpine improves DED symptoms in comparison to placebo or artificial tears as well as a punctal occlusion. While there was no improvement in Schirmer test result, the patients with oral pilocarpine showed better score of ocular staining. Moreover, in SS patients with oral pilocarpine treatment increased the number of conjunctival goblet cells [28, 54, 88, 89]. The oral cevimeline dosage of 20–30 mg every 8 h improved ocular staining scores and TFBUT but no significant differences in lacrimal flow rates were found [28, 54, 90].

Topical secretagogues are approved in treatment of dryness in Japan. Drugs as: 2% rebamipide which increases mucin level over the conjunctiva and cornea (improves TFBUT), 3% diquafosol tetrasodium which increases mucin and fluid secretion (improves ocular staining) are introduced for DED topical treatment in clinical practice [22, 54, 91].

## **6.6 Tear retention**

### *6.6.1 Punctal occlusion*

The idea of punctal/canalicular occlusion is to block tear drainage from the ocular surface and use patients' own tears to maintain the lubrication of the eye. It also helps maintain instilled artificial tears longer [28, 54, 91]. The concept of permanent cautery lacrimal puncta occlusion for DED treatment was described in 1936, first dissolvable implants were used in 1961, but the modern idea of punctal plug use began with Freeman report in 1975 [54, 91–93]. Plugs are made of variety of materials and design, they can be absorbable (last 3 days to 6 months) or non-absorbable. The ideal occluder should be easy to place, block the drainage effectively, be biocompatible, long lasting, easy reversible, and have low potential for infection [28, 54, 91]. Punctal/canalicular plugs are common second-line treatment in aqua-deficiency DED. A comparison of plugs versus artificial tears in patients with SS and DED demonstrated that both treatments improved symptom scores, corneal staining and TFBUT, but Schirmer test and TFBUT were statistically more improved in plugs' group [28, 94].

### *6.6.2 Contact lenses*

Therapeutic contact lenses (TCL) are used to promote corneal healing, protect the ocular surface from the lids and environment, reduce desiccation, and relieve discomfort [22, 28, 54]. Silicone-hydrogel materials have higher oxygen transmission than hydrogels. Some of soft silicone-hydrogel contact lenses are approved for therapeutic wear and could be useful in primary and secondary Sjögren syndrome for relief from discomfort and blurred vision. There is no literature on the use TCL in the treatment of DED in SS, but reports on such a treatment in other entities or ocular surface problems are encouraging [28, 52, 54, 95].

Bandage contact lenses (BCL) are large-diameter, rigid, gas-permeable lenses with scleral fixation. Retention of a fluid reservoir over the cornea and no corneal touch are the reason of the therapeutic effect of BCL. The use of BCL specifically in SS patients is not described, but some patients with SS were included in the groups in which benefit were demonstrated [28, 52, 54, 96].

## **6.7 Mucolytic therapy**

Severe symptoms of eye surface irritation in patients with mucus filaments/strands are the reason to use topical mucolytic solution. Topical N-acetylcysteine (10–20% aqueous solution) therapy for 2–4 weeks usually resolves the problem [28, 97].

## **6.8 Essential fatty acids**

Essential fatty acids (EFA) are polyunsaturated fats that are not synthesized by humans. Dietary supplementation (e.g., fish oil or flax seed oil or nutritional supplements) with omega-3 EFA as anti-inflammatory therapy is considered. Improvement in DED symptoms and signs with both oral and topical omega-3 EFA was described although there is nothing specific regarding the use for SS [22, 28, 97–8]. Gamma-linolenic acid is an omega-6 EFA with anti-inflammatory effect in chronic inflammatory diseases. An inverse association between it and levels of anti-SSA/anti-Ro antibodies were described. Improvement of symptoms and corneal staining after oral supplementation with omega-6 EFA were found [52, 99, 100].

## **6.9 Management of eyelids**

MGD treatment include eyelid hygiene, hot compresses, eyelid massages, thermal pulsation treatment, anti-inflammatory, and antibacterial therapy (e.g., oral tetracyclines and EFA omega-3, topical azithromycin and EFA omega-3 [22, 28, 54, 71, 97, 98, 101]). In patients with MGD, melting point of meibomian lipids rises, which is why hot compresses, warming masks and goggles, infrared heaters, and eyelid massage led to clinical improvement with tear film stability and lipid thickness of the tear film (reduced blockage of meibomian gland excretory ducts and improvement of the meibomian secretion) [32, 54, 71, 101–103]. Tetracyclines are bacteriostatic antibiotics with anti-inflammatory effect (reduction of the synthesis and activity of matrix metalloproteinases, production of IL-1 and TNF- $\alpha$ , activity of collagenases and B-cell activation). A low-dose treatment for 6–12 weeks improves tear film stability, tear production, and symptoms (higher dosages are connected with higher rate of adverse events) [32, 102–105]. Macrolides (azithromycin) have both bacteriostatic and anti-inflammatory effect. They improve meibomian gland function and symptoms, reduce bacterial colonization of eyelid and normalize meibomian gland secretion [32, 106, 107].

To reduce degree of ocular surface exposure for environmental factors and for evaporation a partial closure/closure of the eyelid may be indicated: for short periods, botulinum injections have been used; in other cases, surgical procedures may be considered [28, 108].

## **6.10 Other therapies**

### *6.10.1 Systemic immunomodulatory and biologic therapy*

The treatment with systemic immunosuppression in patients with DED and SS requires clinical trials to assess it [2, 22, 52]. Antimalarials (hydroxychloroquine and chloroquine), in some studies, were found to have benefits for SS DED, but in

others, there was no change (test Schirmer 1, FTBUT) between baseline and the end point; OSDI improved, but there was no statistical difference between treating group and placebo [2, 109–111]. Methotrexate (MTX) has well-documented efficacy in uveitis and scleritis, but there is no data that confirm it works in SS DED: one case report on improvement with MTX therapy [2, 112]. In one open-label study, improvement in symptoms but no changes in signs of DED in patients with pSS treated with mycophenolate mofetil were reported [2, 113]. Rituximab (anti-CD 20 monoclonal antibody) in some studies improved symptoms of DED, in others there was no statistical significance on the final results of ocular dryness and Schirmer 1 testing [2, 52, 114]. There was no improvement in both symptoms and signs after etanercept therapy [52, 115], abatacept (CTLA4-Ig) in some studies improved results of Schirmer 1 test, in others there were changes in FTBUT [2, 116].

### 6.10.2 Hormone therapy

There are some studies on the use of hormonal therapy in patients with DED. Association of low androgen levels with lacrimal gland inflammation and lacrimal insufficiency were found, consequently androgen supplementation could be a potential therapy in DED [97, 117]. Studies on systemic estrogen and estrogen-androgen therapy revealed that estrogen-only therapy may intensify ocular irritation (no benefits in symptoms and signs); however, topical estrogen therapy seems to be beneficial for DED because of the influence on ocular epithelial cells. Combined estrogen-androgen therapy improves symptoms of DED [97, 118–120]. Although dehydroepiandrosterone (DHEA) may replenish suppressed hormonal levels in pSS and improve sicca symptoms, first data on DED symptoms and signs after DHEA therapy have not revealed improvement [95, 121, 122].

### 6.10.3 Others

In literature, we can find some more possibilities of DED treatment in SS patients, but they are published as case reports or clinical studies. Neurostimulation of nasolacrimal pathway stimulates lacrimal gland secretion that improves scores of Schirmer I test and results of ocular staining. A new device for intranasal neurostimulation provides small electrical pulses to stimulate production of patients' tears [22, 123]. Local radiotherapy to the lacrimal gland was reported as a successful treatment in a patient with SS and lacrimal gland involvement [51, 124]. There are experimental studies on topical administration of lacritin (tear glycoprotein with prosecretory, prosurvival, and mitogenic properties) and interleukin-1 receptor antagonist—anakinra (targeting IL-1/IL-1R1 signaling pathway) in aqua-deficiency DED and both of them are promising for future [125, 126]. Therapy with oral lactoferrin (tear protein modulating oxidative stress and regulating microbes) improved corneal sensitivity compared to placebo [52, 127], as well as herbs used in traditional Chinese medicine revealed beneficial effect for symptoms and Schirmer 1 test score compared to placebo [52, 127, 128], but both methods are limited in routine clinic because of the lack of explanation of molecular mechanisms or target limits [52].

## 7. Conclusion

Dry eye disease is an inseparable part of the both types of Sjögren's syndrome. There is no specific test to diagnose it—for everyday practice, several tests are used to diagnose and to interpret the severity of the problem. Moreover, though it is more severe than in other diseases, there is no specific test for DED in SS.



The treatment of DED in SS is also the same as in other patients. Patients are treated with both topical and systemic therapies. There are some trials to use immunosuppressive agents for DED in SS to provide relief to eye dryness symptoms, but there are not enough verified studies on it.

Both in diagnostic and therapeutic problems of DED, there are still challenges for the future and need further multicenter, double-blind, randomized studies.

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