Clinical Guidelines for Management of Dry Eye Associated with Sjögren Disease

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ABSTRACT **Purpose: To provide a consensus clinical guideline for management of dry eye disease associated with Sjögren disease by evaluating published treatments and recommending management options. Design: Consensus panel evaluation of reported treatments for dry eye disease. Methods: Using the 2007 Report of the International Workshop on Dry Eye (DEWS) as a starting point, a panel of eye care providers and consultants evaluated peer-reviewed publications and developed recommendations for evaluation and management of dry eye disease associated with Sjögren disease. Publications were graded according to the American Academy of Ophthalmology Preferred Practice Pattern guidelines for level of evidence. Strength of recommendation was according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines. Results: The recommendations of the panel are briefly summarized herein. Evaluation should include symptoms of both discomfort and visual disturbance as well as determination of the relative contribution of aqueous production deficiency and evaporative loss of tear volume. Objective parameters of tear film stability, tear osmolarity, degree of lid margin disease, and ocular surface damage should be used to stage severity of dry eye disease to assist in selecting appropriate treatment options. Patient education with regard to the nature of the problem, aggravating factors, and goals of treatment is critical to successful management. Tear supplementation and stabilization, control of inflammation of the lacrimal glands and ocular surface, and possible stimulation of tear production are treatment options that are used according to the character and severity of dry eye disease. Summary: Management guidelines for dry eye associated with Sjögren's disease are presented.**

KEY WORDS **Anti-inflammatory agents, autologous serum, corticosteroids, cyclosporine, dry eye disease, mucolytics, omega 3 essential fatty acids, punctal occlusion, therapeutic contact lenses, secretogogues, Sjögren disease**

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I. INTRODUCTION

The Sjögren's Syndrome Foundation initiated development of clinical guideline recommendations for medical practitioners in 2010. Representatives from rheumatology, oral medicine/dentistry, and eye care

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providers were enlisted to evaluate recent literature and develop recommendations for those guidelines. This preliminary perspective from the eye care subcommittee is provided prior to the ultimate publication of the entire committee and is based upon agreement of the subcommittee members, all of whom contributed to the guidelines and agreed upon the recommendations.

The definition of dry eye provided by the 2007 International Dry Eye Workshop (DEWS) report is: "Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[1]

An alternative description of the disease is "dysfunctional tear syndrome" to emphasize that the tear film dysfunction can occur in the presence of normal tear secretion.[2] The discomfort is often described in various ways, such as burning, stinging, grittiness or sensation of something in the eye (foreign body sensation), itching, and, occasionally, pain. A recent survey of the members of the Sjögren's Syndrome Foundation revealed that the symptoms of dry eye were the most annoying and activity-limiting aspect of Sjögren disease. Sjögren disease is an autoimmune disease affecting primarily the exocrine glands of mucous membranes, resulting in dry eye and dry mouth, but often with additional musculoskeletal disturbance and damage to other body systems.[3] Visual disturbance is often noted as fluctuation of vision, particularly during reading or working at a computer, and blinking often clears the vision.

Dry eye is usually classified into two major categories: aqueous-deficient dry eye, in which tear production is reduced, and evaporative dry eye, in which the evaporation of the tear film is abnormally high.[1] Both categories have increased concentration of tear film constituents, as manifested by elevated osmolarity and rapid tear film breakup time (**TFBUT**).[4-7] Although the mechanisms of production of dry eye are easily separated, both conditions often occur simultaneously.

Inflammation of the lacrimal gland and ocular surface occur both as an inciting event in many cases and as a secondary effect as the dry eye disease worsens, prompting the name as keratoconjunctivitis sicca (**KCS**). Further classification of aqueous-deficient dry eye specifies dry eye that is associated with Sjögren disease versus dry eye not associated with Sjögren disease; this is done in recognition of the greater severity of aqueous-deficient dry eye as well as the greater inflammation associated with Sjögren disease.[1,8] It should be noted, however, that aqueous-deficient dry eye and evaporative dry eye have both been associated with Sjögren disease.[9,10]

An additional approach to categorizing dry eye, which has become more frequently used in determining the management strategy, involves the gradation of severity of the dry eye based upon level of discomfort, interference with activities of daily living, degree of clinically observable inflammation, and response to previous therapy.[11]

The literature evaluating the management of dry eye specifically in Sjögren disease is limited, and the options for therapy most often are evaluated in non-Sjögren patients. In this review, the studies that specifically included Sjögren disease patients are identified, although the management options evaluated in non-Sjögren patients are presented when considered essential or helpful in management of Sjögren dry eye disease. Publications were graded according to the American Academy of Ophthalmology Preferred Practice Pattern guidelines for level of evidence (Table 1).

Eye care practitioners frequently encounter patients with dry eye symptoms, as there are more than an estimated 20 million people with dry eye in the United States.[1] Although most patients complaining of dry eye disease do not have Sjögren disease, it is incumbent upon the practitioner to consider Sjögren disease when features of the dry eye suggest it as a possible etiology. More severe disease and more severe inflammation or difficulty in controlling the dry eye should prompt questions about concurrent dry mouth, arthritis, or other systemic evidence of inflammation or autoimmune disease. Patients with these associations should be referred to a dentist and rheumatologist for oral and systemic disease diagnosis and management.

II. EVALUATION OF DRY EYE DISEASE

A. Symptoms

Dry eye is usually symptomatic, although recent studies demonstrate that more than 40% of subjects with clear objective evidence of dry eye disease are asymptomatic.[12] The first diagnostic clue is often the patient's report of either eye discomfort and/or fluctuating vision. Many questionnaires have been developed to assess symptoms of dry eye,

Table 1. Level of evidence of cited publication according to American Academy of Ophthalmology Preferred Practice Pattern guidelines

Parameter	Level of Evidence		
	Level I	Level II	Level III
Overview of Dry Eye			1,2,8,10,11,20
Symptom Evaluation			
Recommended questionnaire		15	13,14
Diagnostic testing			
Tear film breakup time			18,30,31,33
Functional visual acuity			32
Schirmer test		18,33	
Osmolarity	4	12,21,22	9,18
InflammaDry test of MMP9			28
Corneal fluorescein staining			18
Conjunctival lissamine green staining			18
Treatment			
Lubricant drops			41
Hydroxypropylmethyl insert			43
Topical corticosteroid therapy		45	44,46,47,49
Topical cyclosporine		55	54,61,62,63
Essential fatty acids			
Topical			63,65
Oral			SIII (5,6,9,10)
Oral secretogogues	68,69,72	73,74,75	71
Punctal occlusion		76	48,77-81
Autologous serum		85	83
Contact lens therapy		95	

Numbers are reference/citation numbers. "SIII" denotes citation in supplemental on-line material.

but few have been validated as accurate for diagnosis or response to therapy.

Dry eye surveys have been used in a variety of ways in both clinical care and research on dry eye disease. They can be used to screen for dry eye disease, to diagnose dry eye disease, and to monitor changes over time or with treatment. However, a single agreed-upon, validated survey sensitive enough to detect statistically significant changes with treatment or to identify subtypes of dry eye has not been widely adopted. In addition, uniform survey use is not universally accepted, and clinicians and researchers across the globe use different versions or modifications, thereby making it difficult to compare studies.[13,14]

The most frequently used short series of questions are those proposed by Schaumberg and coworkers (Table 2); these three questions have been asked in the largest United States population-based study of dry eye in women and men.[15,16]

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?

The questionnaire was refined and validated by Oden et al, and the two specific symptoms queried, dryness and irritation, are equivalent to asking up to 16 symptom questions.[17] A short symptom questionnaire, based on the evidence in the literature for clinical screening for dry eye in a patient with Sjögren disease is recommended in Table 2.

Table 2. Key screening questions for dry eye disease. A patient reporting 'Yes' to any of the following warrants a full ocular examination

How often do your eyes feel dryness, discomfort, or irritation? Would you say it is often or constantly? (Y/N)
When you have eye dryness, discomfort, or irritation, does this impact your activities (e.g. do you stop or reduce your time doing them)? (Y/N)
Do you think you have dry eye? (Y/N)

More extensive questionnaires often used in clinical trials are summarized in the online supplement to this article (Online Supplement I) and include the McMonnies questionnaire, the Ocular Surface Disease Index (**OSDI**), the Standard Patient Evaluation of Eye Dryness questionnaire (**SPEED**), the Symptom Assessment in Dry Eye survey (**SANDE**), and the Impact of Dry Eye on Everyday Life survey (**IDEEL**).

B. Signs/Tests of Tear Function

Evaluation of the clinical signs of dry eye generally considers three features of the tear film and ocular surface: tear function, tear composition, and ocular surface alterations. The sequence of evaluation of these can influence the subsequent tests; a recommendation of which sequence to use is described at the end of this section.

The simplest tests of tear function are performed by direct observation. The corneal light reflex is a gross measure of the luster and integrity of the tear film. Irregularities of this reflex indicate either instability of the tear film or irregularities of the ocular surface. Observation of the tear meniscus with the biomicroscope provides an indication of the volume of tear film present. The marginal tear strip can be observed with the wide beam of the biomicrocope, or it can be more precisely measured with an optical section or narrow beam of the slit-lamp to determine the height of the tear film meniscus. The marginal tear strip is normally 1 mm in height, but in dry eye it is reduced. Special instruments are available to better quantify the contour and height of the meniscus, and specially designed reflectometers have been used to precisely measure the meniscus volume. These instruments, their use, and the interpretations of observations are accessible in the archive of methodology for diagnosis and evaluation of dry eye that is part of the 2007 DEWS Report and on the Tear Film and Ocular Surface Society (**TFOS**) website (www.tearfilm.org [public domain]).[18]

The biomicroscopic examination also can reveal debris and presence of inflammatory cells in the tear film. If the mucous debris is sufficiently thick, it can be seen to adhere to the ocular surface. Corneal filaments can occur that evoke an uncomfortable or even painful sensation for the patient.[19] The presence of foamy debris, particularly at the lateral canthus, is a sign of concurrent meibomian gland disease, which is the major cause of evaporative dry eye.[20]

Tear film instability is a valuable sign of dry eye disease and can be produced by either aqueous-deficient dry eye or evaporative dry eye or a combination of both mechanisms. The most common method for determining tear film stability is the fluorescein TFBUT that is performed by instilling a small amount of fluorescein dye into the tear film and having the patient blink while being observed through the slit-lamp with incident cobalt blue filtered light. The uniform greenish hue of the fluorescein across the cornea is observed for early breakup, as identified by a dark spot forming in the tear film.[18] Normal TFBUT is greater than 10 seconds. Rapid tear film breakup is an indicator of tear instability that can be due to dry eye or ocular surface irregularities. There are instruments that allow noninvasive evaluation of tear breakup.[18]

Determination of tear secretion rate differentiates aqueous-deficient dry eye from evaporative dry eye, and is most frequently done clinically by use of the Schirmer tear test strip or the phenol red thread test.[18] The Schirmer test is performed by placing a small strip of filter paper of known dimension (5 x 35 mm) on the margin of the lower eyelid at the junction of the lateral and middle third of the lid and leaving it in place for 5 minutes, then measuring the length of the strip that is wet with tears. If this test is done without prior instillation of topical anesthetic, it is a measure of reflex secretion of tear (Schirmer 1 test); if the test is done following instillation of a topical anesthetic, it is a measure of baseline tear secretion (basal tear secretion test). The normal value of the Schirmer 1 test is greater than 10 mm of wetting, but cutoff referent values for dry eye have been recommended as 5 mm of wetting.[18] Some clinicians use a value of 7 mm with the Schirmer 1 test and 3 mm for the Schirmer with anesthetic. The phenol red thread test is performed by placing a small thread impregnated with phenol red dye on the lower eyelid margin and measuring the amount of wetting of the thread after 15 seconds. The normal value of the phenol red thread test is greater than 10 mm of wetting.[18] A more sensitive measure of tear secretion can be obtained with research instruments such as the fluorophotometer, but this is not routinely available in the clinical setting.

Measurement of the composition of the tear film is a valuable method of diagnosing and monitoring dry eye, but the methods for performing such measurements have previously been limited to the research setting.[4] Elevated osmolarity of the tear film is a hallmark and defining feature of dry eye disease, but previous methods of measurement have

been laborious and time-consuming. Recent availability of an in-office instrument for determination of tear film osmolarity has allowed more clinical application of such technology.[21]A new tear osmometer (TearLab Corp, San Diego, CA) has been approved by the FDA for marketing in the United States.[22] This same technology is available in Europe and Canada and is in clinical trials in Japan. The device uses a disposable tip (lab on a chip), which collects a 50 nL sample upon contact with the inferior lateral marginal tear strip. The tears are collected in a microchannel, and tear osmolarity is measured using electrical impedance within 3 seconds. The collecting pen and chip are inserted into a desktop unit, and the osmolarity value is displayed within 10 seconds. Results obtained with this technology have been shown to be equivalent to those obtained with laboratory instruments requiring much larger samples, transfer of samples, and more than 15 minutes to perform.

In a multi-site clinical study of 299 subjects, tear osmolarity alone, compared to the most commonly performed objective tests for the diagnosis of dry eye disease, showed a linear relationship to increasing severity of disease measured using a composite index of severity across the entire range of severity.[22] In addition, tear osmolarity has a positive predictive value in the diagnosis of dry eye disease of 86%, the highest of all the objective measures tested.[21,22] Measurement of both eyes is recommended due to the transient effects of compensatory mechanisms that lower tear osmolarity in the early stages of dry eye disease. These effects are seen asymmetrically, and the higher value is reflective of disease effects; this variability is not seen in subjects without dry eye disease.

Measurement of the levels of inflammatory mediators in the tear film serves to identify the contribution of inflammation and the severity of dry eye disease. Levels of inflammatory mediators in the tear film and conjunctiva correlate with severity of ocular surface disease. Inflammatory cytokines produced by ocular surface epithelial cells and leukocytes that invade the conjunctiva cause ocular surface epithelial disease. Interferon gamma (**IFN-γ**) and interleukin (**IL**)-1 promote conjunctival squamous metaplasia with accompanying decrease in the number of mucus-producing goblet cells.[23,24] IL-17 stimulates production of proteases that cause loss of the superficial corneal epithelium, leading to an irregular and poorly lubricated corneal surface.[25,26] Increased production and activity of matrix metalloproteinase (**MMP**)-9 has been measured in dry eye and other ocular surface disorders.[27] A recently available device approved for use in Canada, Europe, and the United States is able to determine the presence of MMP-9 in tears in a clinical setting.[28]

Evaluation of the ocular surface is most frequently performed clinically with the instillation of topical dyes to determine the integrity of the epithelial layers of the cornea and conjunctiva.[18] Fluorescein is the most commonly used dye to determine integrity of the corneal epithelium and is conveniently observed after measurement of the fluorescein TFBUT. Rose bengal and lissamine green are the two dyes most often used for evaluating the integrity of the conjunctiva.[18] Both dyes stain the same features of the ocular surface, including mucus strands, filaments, and areas of epithelium unprotected by normal mucin components of the glycocalyx. A classic pattern of interpalpebral staining across the medial conjunctiva, cornea, and temporal conjunctiva occurs in advanced dry eye disease, but early staining is more often on the inferonasal cornea, with central staining occurring later. Conjunctival staining usually occurs before corneal staining, and medial staining often occurs before temporal conjunctival staining. Instrumentation using computer-analyzed reflections from the ocular surface also has been used to noninvasively evaluate tear stability and corneal surface smoothness. Following a blink, tear instability and superficial corneal epithelial disease cause greater distortion and more rapid distortion of rings reflected off the corneal surface.[29-31] Greater corneal surface irregularity correlates with reduced contrast sensitivity and functional vision.[32]

Evaluation of lid function and lid margin disease is critical in the evaluation of dry eye, particularly since impaired lid function can disrupt the spreading of the tear film and lid margin disease is the most common cause of evaporative dry eye. Examination of the eyelid margin for evidence of debris, erythema, and swelling can indicate anterior blepharitis, which can mimic dry eye symptomatically. Expression of the meibomian glands and observation of the character of secretion can establish the diagnosis of meibomian gland dysfunction, the most common cause of evaporative dry eye.[20] Meibomian gland dysfunction is often associated with decreased stability of the tear film.

Since the above-described methods for evaluating the signs of dry eye disease can influence the results of the subsequent tests, it is important to consider the sequence of performance of the tests. The general principle is to perform the least invasive tests before performing the more invasive tests. Direct observation without any manipulation of the eyelids, tear film, or ocular surface is first performed. Next, osmolarity is measured, using a protocol that obtains samples from the inferior and lateral tear meniscus and does not increase reflex tear secretion. Instillation of topical fluorescein and distribution of the dye with several complete blinks is quickly followed by measurement of the TFBUT. After 1.5-3 minutes from the time of fluorescein instillation, the determination of any corneal staining is recorded, and measurements should be completed by 4-5 minutes. Lissamine green is instilled, and observations are made after 1 minute but before 4 minutes to obtain optimal results. The Schirmer 1 test or phenol red thread test is then performed after any residual dye is blotted from the meniscus. Schirmer test with anesthesia can be performed to determine the level of unstimulated (basal) tear production.

III. MANAGEMENT OF DRY EYE

The management approach to dry eye disease has changed over the past 10 years, but several principles persist. Communication between the practitioner and the patient is

critical to assure that the patient understands the disease, the aggravating factors, and the management strategy. Given the multiple contributing causes of dry eye and the expansion of therapy to include nutritional support and management of lid margin disease, in addition to topical therapy, the patient should consider therapy of dry eye as part of their overall health management.

In general, therapy is based upon the severity of the dry eye disease and the patient response to each added therapy. A recent study has proposed that severity of disease is best seen not in discrete categories but rather as a continuous scale described by different clinical tests, each of which provides important independent information. This is a mathematical equivalent of what clinicians commonly do to characterize a disease, i.e., perform several tests measuring different aspects of the disease along with clinical examination to make an overall assessment of severity. Tear osmolarity has been shown to parallel increasing severity over the entire range of dry eye disease.

Some patients with mild, episodic dry eye can be managed with modification of their environment and activities of daily living. Avoiding systemic medications that can reduce tear secretion, such as systemic antihistamines and tranquilizers with anticholinergic effects, can help maintain adequate tear secretion. Maintaining eyelid margin hygiene to reduce anterior blepharitis and meibomian gland dysfunction may reduce symptoms. Avoiding smoking and maintaining a healthy diet with supplemental omega 3 essential fatty acids may reduce the severity of dry eye. Avoiding, when possible, very dry or windy environments is helpful. Lastly, limiting certain tasks associated with reduced blink rate, such as reading or using a video display terminal for prolonged periods, may reduce or help control symptoms. However, when such preventive measures are inadequate to control episodic or chronic dry eye, there is a logical sequence of therapies that can be used.[33-37]

A. Topical Tear Substitutes and Lubrication

The first line of therapy for dry eye in Sjögren disease has been volume replacement and lubrication with "artificial tears." These products do not mimic the exact composition of human tears. Their main ingredients are lubricants with a polymeric base or viscosity agent. The ingredients are intended to add volume to the tear lake, as well as to increase the residence time of the tear supplement on the ocular surface. The lubricants may also cushion the ocular surface, reducing friction between lid and globe, and provide additional comfort in the dry eye condition.

Tear supplements have varied formulations.[38] Some tear substitutes add electrolytes, which are present in normal tears, to help prevent ocular surface damage. Potassium and bicarbonate ions are important for surface ocular health and are included in Bion Tears® (Alcon, Inc, Ft Worth, TX) and Theratears® (Advanced Vision Research/Akorn, Lake Forest, IL). Because bicarbonate is not stable (breaking down into water and carbon dioxide), these formulations are packaged in foil.

Dry eye patients have elevated tear osmolarity.[9,21,22] This causes both corneal and conjunctival surface changes, because the hyperosmotic tear film is pro-inflammatory.[39] HypoTears® (Novartis, Duluth, GA) and Theratears® are hypotonic artificial tears based on this principle. Optive® (Allergan, Inc, Irvine, CA) is a tear supplement formulated with compatible solutes (e.g., glycerin, erythritol, and levocarnitine) that distribute between the tear film and intracellular fluid in a way that protects against the effects of hyperosmolarity of the tear film.

The main component of most supplemental tear preparations is the viscous agent. These are macromolecular complexes that increase the residence time of the supplement in the tear film. Depending on the viscosity of the lubricant, the supplement may cause blurred vision. The common base polymers in tear supplements are carboxymethylcellulose and hydroxymethylcellulose. Systane® (Alcon, Inc., Fort Worth, TX) contains hydroxypropyl-guar (HP-guar), a gelling agent that has been combined with glycol 400 and propylene glycol to prevent corneal desiccation.

In addition to viscous agents, certain tear supplements attempt to mimic the lipid component of tears. Refresh Optive Advanced (Allergan) contains castor oil and is labeled "lipid enhanced to retard evaporation." Mineral oil is a major component of SootheXP®(Bausch and Lomb, Rochester, NY). Systane Balance®(Alcon) has a lipid emulsion in addition to the HP-Guar to stabilize the lipid layer of the tear film. A combination of mineral oils is used in Retaine MGD® (Ocusoft; Richmond, TX). Since the type of phospholipid contained in a formulation affects the tear film stability and film-forming ability, a neutral or negatively charged phospholipid is preferable to a positively charged molecule, which may act to disrupt tear film formation.[40]

Hyaluronic acid is a highly hygroscopic viscous agent that has surface coating properties and is a component of many tear products outside the United States. It has a prolonged residence time for ocular surface protection and lowers tear osmolarity with extended use.[41] It is a component of Blink Tears® (AMO, Abbott Park, IL), Blink Gel Tears®(AMO), Oasis TEARS® (Oasis Medical, Glendora, CA), and Oasis TEARS Plus®.(Oasis Medical).

Although almost all tear supplements are available over the counter (**OTC**), one preparation requires a prescription, FreshKote® (FOCUS Laboratories, North Little Rock, AR). It is indicated for moderate-to-severe dry eye and contains polyvinyl pyrrolidone 2%, polyvinyl alcohol (87% hydrolyzed) 0.9%, polyvinyl alcohol (99% hydrolyzed) 1.8%, and proprietary Amisol® CLEAR (a phospholipid). It does have preservatives, EDTA and Polixetonium. This tear supplement solution has a lipid-containing formulation as well as a high oncotic pressure (65 mmHg). High oncotic pressure is protective of the epithelial surface.[42]

Among the wide variety of tear supplements, none is clearly superior. Head-to-head studies may show some comparative improvement in symptoms and objective signs. As a general principle, the thicker preparation has a longer residence time but is more likely to blur vision. Gels are

more viscous than solutions. Preservative in the tear supplements have an impact on the ocular surface. Benzalkonium chloride and EDTA are potentially toxic to the ocular surface. The toxicity of preservatives increases with more frequent use, and dry eye patients, because of decreased tear volume, are more susceptible to preservative toxicity. Therefore, when supplemental tears are used more than 4-6 times a day, preservative-free unit dose vials are recommended.

Ophthalmic ointments are the thickest of lubricants used to protect the ocular surface. Ointments adhere to the surface longer than either artificial tear or gel supplements. They are typically used before bedtime to provide relief of dry eye symptoms, enabling sleep. Their thickness may produce more blurred vision than tear supplements. Ophthalmic ointments typically are composed of white petrolatum and mineral oil, as well as lanolin alcohols and liquid lanolin.

Another option for long-acting ocular surface lubrication is the hydroxypropyl cellulose insert.[43] Lacrisert® (Aton Pharmaceuticals, Lawrenceville, NJ) is a 5 mg insert of preservative-free hydroxypropyl cellulose. The insert is placed in the inferior cul-de-sac and dissolves at body temperature, thickening the tear film. Patients must be instructed about the proper placement. Lacrisert® may decrease the need for frequent topical tear supplementation. The thickened tear film may cause some blurred vision. Typically, morning insertion provides once-daily dosing, but insertion at the time of sleep sometimes provides better performance. However, some patients may prefer to use a second insert if necessary. Some will use the insert at bedtime instead of ointment. A full tabular summary of the available OTC tear preparations is listed in the online supplement to this article (Online Supplement II).

B. Anti-inflammatory Therapy

Recent studies have shown that in KCS, an inflammatory response is present on the ocular surface.[23-25] If the inflammatory reaction is controlled, then the signs and symptoms of KCS should improve. This provides the rationale for considering anti-inflammatory drugs in the treatment of patients with Sjögren disease with moderate or severe ocular surface disease.

1. Topical Corticosteroids

Multiple studies have shown the clinical value of short-term use of topical steroids in managing patients with KCS. In a retrospective case series study of 21 patients with moderate-to-severe ocular surface disease who were symptomatic despite maximum aqueous enhancement therapy, Marsh and Pflugfelder found a significant decrease in irritative symptoms after 2 weeks of topical nonpreserved methylprednisolone. In addition, there was a decrease in corneal fluorescein scores (2.6 +/-0.5 points on a 12-point scale) and resolution of filamentary keratitis. Elevated intraocular pressure and posterior subcapsular cataracts occurred in patients receiving the corticosteroids longer than 3 months.[44] Similar results were observed in a subsequent study in a loteprednol-treated group after 2 weeks of therapy, but the difference between the loteprednol-treated and the vehicle-treated groups did not reach statistical significance at 4 weeks.[45]

In a study of 60 patients with moderate or severe dry eyes, Yang and Sun reported good response to topical steroids.[46] All of the patients were using artificial tears four times a day. Topical 0.1% fluorometholone was then added to the regimen four times a day. After 1 week, there was a decrease in symptoms (6.95 +/-1.11 to 4.08 +/-1.09, $P<.05$). After 1 month, there was a significant improvement - ($P<.05$) in fluorescein staining, TFBUT, and conjunctival hyperemia. In addition, the Schirmer measurement increased an average of over 2 mm ($P<.05$). In this study, no complications associated with topical corticosteroid therapy were reported.[46]

Hong et al treated 53 patients with Sjögren disease with topical nonpreserved methylprednisolone for 2 weeks, then tapered off the medication every 2 weeks until discontinuation demonstrated a significant reduction ($P<.001$) in fluorescein staining and improvement in TFBUT and Schirmer test measurements. They also noted increase in periodic acid-Schiff-positive cells indicative of mucin secretory goblet cells. After the initial therapy, the mean time before additional treatment was required was 56.6 weeks, with 20.8% of the patients having recurrence. After a second pulsed therapy with methylprednisolone, the mean time before treatment was 72.4 weeks, with only 1% recurring. There were no complications related to the steroid therapy during this long-term treatment. This study suggests that using topical steroids as a pulse therapy may be safe and effective in treating moderate-to-severe Sjögren disease.[47]

In a prospective study of 30 patients, 15 patients (group 1) received non-preserved topical steroids for 2 weeks prior to punctal occlusion, and 15 patients (group 2) received punctal occlusion alone.[48] At 1 week and at 2 months after punctal occlusion, the group 1 patients had a significant decrease in symptom severity compared to the group 2 patients.[48] The group 1 patients also had a marked decrease in corneal staining compared to their pre-occlusion staining. In a single-masked, randomized, prospective clinical trial, Avunduk et al compared treatment in three groups of patients with moderate-to-severe KCS. Group 1 received artificial tear substitutes; Group 2 received artificial tears and non-steroidal anti-inflammatory drops; and Group 3 received artificial tears plus topical corticosteroid drops. The patients in Group 3 had significantly lower symptom severity scores and fluorescein and rose bengal staining. On days 15 and 30, they had significantly higher numbers of periodic acid-Schiff positive (goblet) cells on impression cytology and lower numbers of inflammatory cells.[49] Another study by Lee et al reported that 0.1% prednisolone lowered tear nerve growth factor levels (elevated in ocular inflammation), improved patient impression cytology scores, and decreased symptom scores.[50] Topical steroids, given 2-4 weeks prior to starting Restasis® (Allergan, Irvine,

CA) may decrease the associated burning and stinging associated with the drug.[51]

The studies summarized above, although limited in number, show that topical corticosteroids are effective in decreasing the signs and symptoms associated with moderate-to-severe KCS. However, the possible complications associated with longterm usage, such as cataracts, glaucoma, and infection, would limit their use to short-term or pulse therapy to treat patients with moderate-to-severe disease that is not controlled with other therapies. For such patients, a 2-4 week course could be considered. It is possible that the newer topical steroid preparations may have less potential for raising intraocular pressure or causing cataracts, although there are no large-scale studies that confirm this speculation.

2. Topical Cyclosporine

Since its approval by the FDA in December 2002, topical cyclosporine (Restasis®) has been used to treat dry eye disease.[52] Although the mechanism of action was initially thought primarily to inhibit activation of T-lymphocytes, further study has confirmed that it has multiple inhibitory properties, including the ability to inhibit apoptosis in other cell types.[53]

Topical cyclosporine is formulated as a lipid emulsion of castor oil that also includes glycerin, polysorbate 80, and sodium hydroxide (to adjust the pH) and is much better tolerated than previous oil-based formulations. It has no preservative and is dispensed in unit dose ampules. Restasis® is marketed in a 0.05% emulsion. It is one of only two FDA-approved drugs for the treatment of dry eye, the other being the dissolvable Lacrisert™ (Aton Pharma, a division of Valeant Pharmaceuticals North America).

Cyclosporine is a calcineurin inhibitor that has been evaluated in patients with aqueous-deficient dry eye disease (chronic dry eye). After excellent tolerance results in Phase 1 clinical trials, Phase 2 trials were conducted in 90 patients with moderate-to-severe dry eye (Schirmer <5 mm/5 min; corneal punctate fluorescein staining >4 of a possible 15; symptoms >2 of a possible 4) with dosing twice daily. The trial used a randomized, double-masked, placebo-controlled design, with dose-ranging topical cyclosporine (either 0.05, 0.1, 0.2, or 0.4%) given twice daily for 12 weeks.[54] No clear dose response relationship was demonstrated, but the cyclosporine 0.05% and 0.1% emulsions produced significant improvements from baseline in symptoms and in corneal fluorescein and rose bengal staining. Combined results from two larger randomized, double-masked, placebo-controlled Phase 3 trials analyzed 877 moderate-to-severe dry eye patients who instilled cyclosporine 0.05% (n=293), cyclosporine 0.1% (n=292), or the emulsion vehicle (n=292) twice daily for 6 months.[55] Cyclosporine 0.05% provided the most consistent improvement, but the emulsion vehicle showed surprisingly effective reduction in some signs and symptoms, particularly in the early follow-up period. This prominent vehicle effect did not show statistically significant difference between vehicle and active drug, but the encouraging response to the vehicle prompted subsequent marketing of the vehicle as a tear-stabilizing lubricant with prolongation of TFBUT.[55]

Patients treated with cyclosporine 0.05% emulsion showed significantly greater improvement in blurred vision than vehicle-treated patients and decreased frequency of supplemental artificial tear use compared with those in the vehicle group ($P \leq .006$). Cyclosporine 0.05% reduced punctate corneal fluorescein staining better than vehicle at 4 and 6 months of treatment ($P=.044$ and $P=.008$, respectively). Increase in tear production as assessed by Schirmer testing (with anesthesia) was significantly greater in the cyclosporine 0.05% group than in the vehicle group ($P \leq .009$). Despite the observation that stinging upon instillation occurred in 17% of patients, only 3% of patients were intolerant to the cyclosporine emulsion. No superinfection, allergic reaction, or other significant adverse effect was seen.[55]

Further subset analysis of the beneficial effect of cyclosporine on tear production in patients who were not concomitantly treated with other anti-inflammatory therapy or previously treated with punctal plugging was presented to the FDA, which approved the 0.05% cyclosporine emulsion for the indication of reduced tear production presumed to be due to inflammation. Improvement in tear production was seen in 59% of patients, with 15% demonstrating 10 mm or more increase in Schirmer test measurement (data on file, Allergan Inc, NDA).

In addition to the improved clinical outcome, immunohistological improvement of the ocular surface occurred with topical cyclosporine therapy, including reduction of cell surface markers of activated T-lymphocytes and apoptotic cells in conjunctival biopsies.[56,57] Cyclosporine treatment also reduced expression of a pro-inflammatory cytokine and increased goblet cell densities toward normal in the conjunctival epithelium of dry eye patients. Treatment of dry eye with cyclosporine 0.05% was significantly more effective in reducing histocompatibility HLA-DR levels on epithelial cells than treatment with vehicle ($P \leq .034$).[57] A second study also demonstrated significant reductions of HLA-DR and a marker of activated T-cells, CD11a, in conjunctival biopsies from dry eye patients following 6 months of cyclosporine 0.05% treatment ($P \leq .05$).[58] In a study evaluating the effects of sequential artificial tear therapy followed by cyclosporine, no change in goblet cell density was observed after 4 weeks of preservative-free artificial tear use, while goblet cell density was significantly greater than baseline in the inferior bulbar conjunctiva after 6 weeks of cyclosporine therapy and significantly greater in the inferior and temporal bulbar conjunctiva after 12 weeks of cyclosporine therapy.[59]

The recommended therapy is topical application of one drop of cyclosporine in each eye twice daily.[60] There is a 17% incidence of stinging upon instillation, but use of topical corticosteroid applied concurrently reduces the intolerance, speeds suppression of inflammation, and can be

discontinued after 2 weeks.[51] Long-term safety of topical cyclosporine has been confirmed in a 3-year follow-up study.[61]

The use of topical cyclosporine in treating evaporative dry eye due to meibomian gland dysfunction has been advocated in the literature and is a recommendation of the International Tear Film and Ocular Surface (**TFOS**) Workshop on Meibomian Gland Dysfunction.[20] Obstruction of meibomian gland orifices, whether by squamous epithelial metaplasia or solidified lipids, causes decreased function of tear lipids with instability of the tear film, increased evaporation of the tear film, and ocular irritation. Traditional treatments for posterior blepharitis and meibomian gland dysfunction include lid hygiene and massage following application of hot compresses, low dose oral tetracyclines, and use of topical antibiotics to decrease bacterial colonization of the lid margins.

In a prospective, randomized, double-masked, placebo-controlled study, 33 patients diagnosed with meibomian gland dysfunction were treated with either cyclosporine (0.05%) or unpreserved artificial tears BID, and were encouraged to practice good lid hygiene.[62] At 3 months the cyclosporine-treated patients had a greater decrease in the number of obstructed meibomian gland inclusions than the patients treated with artificial tears (P=.001). Vascular injection and telangiectasia were reduced more in the cyclosporine group than in the placebo group (P=.001 and P=03, respectively). The mean corneal fluorescein staining score in the cyclosporine group also decreased significantly compared to the placebo group (P=.01). No statistically significant changes were documented in lissamine green staining of the conjunctiva and mean Schirmer scores.

A prospective, randomized study of 30 consecutive patients with posterior blepharitis evaluated treatment by topical administration of cyclosporine 0.05% or a combination of tobramycin 0.3%/dexamethasone 0.1%. Improvements from baseline in the viscosity of meibomian gland secretions, TFBUT, and Schirmer scores were all significantly greater (P<.015, P<0.018, P<.001, respectively) for cyclosporine-treated patients than for those treated with tobramycin/dexamethasone.[63]

3. Omega 3 Essential Fatty Acids

Among the treatments considered in the anti-inflammatory category are essential fatty acids, particularly omega 3 fatty acids.[64] Essential fatty acids are polyunsaturated fats that humans cannot synthesize and therefore must take in through diet and/or nutritional supplements. Essential fatty acids are divided into two groups: omega 6 and omega 3, named by the location of the first double bond in the carbon chain. Key to understanding the role of essential fatty acids in human physiology is that both omega 3 and 6 are digested by the same enzymes: 1) omega 6 to linoleic acid, gamma linolenic acid, dihydro-gamma-linolenic acid, and arachidonic acid and eicosanoids (most associated with increased inflammation); 2) omega 3 to alpha linolenic acid, eicosapentanoic acid and docosahexanenoic acid, eicosansoids and resolvins (most associated with a decrease in inflammation).

Which metabolites of essential fatty acids are predominant for a given person depends on diet: the more omega 6, the more inflammatory metabolites; the more omega 3, the more anti-inflammatory metabolites. Today in the typical Western diet, omega 6 predominates (6 to 1); some suggest the optimal diet should have equal omega 6 and 3 (1:1). To counter the effects of current dietary intake, it has been suggested that increased omega 3 supplementation would be useful and would have anti-inflammatory effects. Clinical research suggests that omega 3 intake can help decrease heart disease and improve rheumatoid arthritis, although research is still underway to determine level of efficacy for these diseases. Following this reasoning, omega 3 intake has been recommended for patients with dry eye disease, given the role of inflammation in dry eye disease.[64,65]

The evidence that essential fatty acids are useful in treatment of dry eye disease is sparse. The studies supporting their use are summarized in Section III in the online supplement to this article. New research is underway to determine the efficacy and safety of omega 3 supplementation in dry eye disease, using a large, double-masked, randomized, multicenter clinical trial (DREAM trial: https://clinicaltrials.gov/ct2/show/NCT02128763?term=dream&rank=5).

Essential fatty acids in general are considered a low-risk dietary supplement. Patients taking more than 3 grams of omega 3 fatty acids from capsules should do so only under a physician's care. High intakes could cause excessive bleeding in some people. It is reasonable to follow the recommendations of the American Heart Association, which are provided in the online supplement to this article[66] (Online Supplement III).

C. Secretogogue Therapy

A secretagogue is a substance that causes another substance to be secreted. Oral pilocarpine and cevimeline are lacrimal and salivary gland secretagogues that stimulate secretion of lacrimal gland fluid (tears) and saliva. They are commercially available under the respective brand names Salagen® (MGI Pharma, Bloomington, MN) and Evoxac® (Daiichi Sankyo, Edison, NJ) and act on the lacrimal and salivary gland M3 muscarinic receptors. Salagen® is indicated for the treatment of symptoms of dry mouth 1) from decreased salivary gland secretion due to radiotherapy for cancer of the head and neck; and 2) in patients with Sjögren disease. Evoxac® is indicated for the treatment of symptoms of dry mouth in patients with Sjögren disease. The recommended dose for Salagen® tablets is 5 mg taken four times a day and for Evoxac® 30 mg taken three times a day.

Although neither Salagen® nor Evoxac® has been approved by the U.S. Food and Drug Administration for the treatment of dry eye, several studies show some effectiveness in the treatment of dry eye in patients with Sjögren disease. Oral pilocarpine (Salagen®) at dosages of

10-30 mg/day improves dry eye symptoms. Two placebo-controlled trials evaluated oral pilocarpine for the treatment of dry eye in Sjögren disease. The largest trial (373 subjects) evaluated doses of 2.5 mg and 5.0 mg given every 6 hours.[67] A higher proportion of subjects in the 5.0 mg group had improvement of dry eye symptoms than in the placebo group (42% vs 26%, P≤.009), but not in the 2.5 mg group. The second trial (256 subjects) compared 5 mg against a dose-escalating regimen of 5.0-7.5 mg every 6 hours.[68] Only minimal improvement in ocular symptoms occurred in the 5.0 mg group; however, significant improvement was noted in the dose-escalating group (53% vs 26%, P<.001). A third study (85 subjects) compared oral pilocarpine (5 mg) against artificial tears and punctal occlusion.[69] Ocular symptoms were significantly improved in the oral pilocarpine group compared to the artificial tear (p<.001) and the punctal occlusion (p<.05) groups. While there was no improvement in Schirmer 1 tests among the three groups, subjects treated with pilocarpine showed a greater improvement in rose bengal staining compared to the other two groups (P<.05). Human conjunctival goblet cells also contain muscarinic receptors,[70] and in patients with Sjögren syndrome, oral pilocarpine has been shown to increase the number of human conjunctival goblet cells.[71]

In the largest trial,[67] the most common adverse effects were sweating (5 mg, 43.3%; 2.5 mg, 10.7%, placebo, 7.2%), urinary frequency (5 mg, 9.5%; 2.5 mg, 10.7%, placebo, 1.6%), flushing (5 mg, 9.5%; 2.5 mg, 1.7%, placebo, 1.6%), and increased salivation (5 mg, 2.4%; 2.5 mg, 0%, placebo, 0%). In the second trial,[68] 23% of the subjects switched from 7.5 to 5.0 mg every 6 hours because of adverse effects (sweating, urinary frequency, flushing, and chills). Similar side effects were reported in the third study.[69]

Four placebo-controlled trials have evaluated oral cevimeline (Evoxac®) in the treatment of dry eye in Sjögren disease. The largest trial (197 subjects) evaluated 15 mg and 30 mg every 8 hours and found significant improvement in overall dry eye symptoms in the 30 mg group compared to placebo (66% vs 36%, P=.0002).[72] There were significantly greater (increased) differences in lacrimal flow rate between the 15 mg group and the placebo group (P=.0324) and the 15 mg and 30 mg group (P=.0475). In the second trial (75 subjects), doses of 30 mg and 60 mg every 8 hours were compared.[73] Overall dry eye symptoms improved significantly in both the 30 mg and 60 mg groups (P=.004 and 0.03, respectively). No significant differences in lacrimal flow rates were found. The third trial (60 subjects) found significant improvement in dry eye symptoms (P=.046), tear dynamics (P=.031) and in global improvement in the 20 mg (every 8 hours), but not the 30 mg (every 8 hours) group.[74] Rose bengal scores, fluorescein scores, and TFBUT were significantly improved for both groups at various time points throughout the study. A fourth trial (44 subjects) found no significant differences in dry eye symptoms compared to placebo with a dose of 30 mg every 8 hours.[75] In the largest trial,[72] nausea was more frequent in the 30 mg group than in the placebo group (21% vs 7.1%, P= .0209). Increased sweating was also more common in the 30 mg group than in the placebo group (17.7% vs 1.4%, P=.0011). In the second trial,[73] increased sweating, nausea, and rigors were more common in the 60 mg group than in the placebo group (67% vs 9%, P<.001; 52% vs 0%, P<.001; and 30% vs 4%, P=.03, respectively). In general, for both medications, the improvement in dry mouth symptoms was greater than in dry eye symptoms. Oral pilocarpine at a dose of 5 mg every 6 hours produced improvement in dry mouth symptoms in 61% (vs 31% placebo) compared to a 42% (vs 26% placebo) improvement in dry eye symptoms.[69] Oral cevimeline, 30 mg every 8 hours, improved dry mouth symptoms 66% (vs 37% placebo) and 39% (vs 24% placebo).[73]

In summary, both oral pilocarpine and cevimeline have been shown to be effective in reducing dry eye symptoms, and in some studies, effective in improving objective findings of dry eye. These medications, however, seem to have greater effect on dry mouth symptoms than dry eye symptoms. The predominant side effect of both medications is sweating.

D. Punctal Occlusion

Punctal occlusion, the blockage of the tear drainage system at the level of the puncta or canaliculus, helps preserve ocular surface tears or instilled artificial tears. While there are no large-scale, prospective-controlled clinical studies on the efficacy of punctal occlusion,[76] reports in the literature for over 30 years strongly suggest that punctal occlusion can help decrease the signs and symptoms associated with KCS.[77-80] A comparison of punctal plugs versus artificial tears in the treatment of patients with keratoconjunctivitis and Sjögren disease demonstrated that both treatments greatly improved OSDI, corneal fluorescein staining, Schirmer test, and TFBUT scores compared to pretreatment levels. However, only the values of the Schirmer test scores and TFBUT were statistically more improved than the scores in the artificial tear group.[81] Punctal occlusion can be performed on a temporary or permanent basis. The various methods are summarized in the online supplement to this article (Online Supplement IV).

E. Autologous Serum

The use of topical autologous serum to treat ocular surface damage from dry eye is usually reserved for the most severe cases that have not responded to other treatments, including intensive lubricant and anti-inflammatory therapy. It was first reported to improve dry eye symptoms and signs in 1984.[82] Despite lack of regulatory approval, autologous serum (20% topical solution) is now documented in numerous reports to have confirmed benefit in a variety of patients suffering ocular surface disease, including Sjögren disease,[83] graft-versus-host disease, Stevens-Johnson syndrome, cicatricial pemphigoid, and other conditions.[84] Autologous serum contains fibronectin, vitamin A, cytokines, and growth factors, as well as anti-inflammatory substances, such as interleukin receptor antagonists and

inhibitors of matrix metalloproteinases. It is not clear which of those constituents is most helpful, but significant improvement in symptoms, fluorescein TFBUT, and rose bengal staining scores have been reported compared with artificial tears.[85]

The disadvantages of using autologous serum include the nuisance of preparation, the need to refrigerate the drops, and the potential risk of infection if contamination of the solution occurs.[86] The stability of frozen autologous serum has been verified, however, for up to 3 months.[85] Typically, the serum is applied topically four times daily, and this can be done in conjunction with other therapy.

Topical autologous plasma has been reported to improve corneal epithelial healing and improve corneal nerve morphology and function in patients with neurotrophic keratopathy.[87] It has also been tested in dry eye disease.[88]

F. Mucolytic Therapy

When mucus strands or filaments are present on the cornea, symptoms of irritation can be severe enough to justify therapy with topical mucolytic solutions.[35,36] Topical N-acetylcysteine is not commercially available but can be prepared by compounding pharmacies, usually as 10-20% aqueous solutions (e.g., Leiter's Pharmacy, San Jose, CA). Topical application three times daily will usually resolve the problem within 2 weeks. Although the drops may sting on instillation and have an odor of sulfur, both are usually tolerated for the 2-4 weeks of therapy required.

G. Therapeutic Contact Lenses

Contact lenses are recommended in the 2007 Report of the International Dry Eye WorkShop (DEWS) as a treatment for dry eye, Severity Level 3, along with serum and permanent punctal occlusion, if Level 1 and Level 2 treatments are inadequate.[11] There is no literature specifically on the treatment of the ocular manifestations of Sjögren disease with therapeutic contact lenses, but reports on treatment of other entities, or of ocular surface disease in general, are perhaps relevant. The goal of therapeutic contact lenses in Sjögren disease, as in all types of ocular surface disease, is to promote corneal healing, protect the ocular surface from the lids and environment, reduce desiccation, and relieve discomfort.

Several silicone-hydrogel soft contact lenses are FDA-approved for therapeutic extended wear, and these can be useful in the relief of the discomfort and blurry vision in primary and secondary Sjögren disease.[89] Silicone-hydrogel materials have higher oxygen transmission than hydrogels and are preferred on a theoretical basis. Poor retention might require the use of very large diameter soft lenses that are available only in hydrogel materials. Russo et al reported on the safety and efficacy of extended wear silicone-hydrogel soft lenses in the treatment of ocular chronic graft-versus-host disease in seven patients. Improvement was achieved in best corrected visual acuity and in symptoms (based on the OSDI), and no adverse events or complications were observed. These patients were studied for only 1 month, and the investigators advised that further study is warranted with a larger sample size including various causes of dry eye disease for a longer study period to verify the safety of this treatment modality. It is not clear that silicone-hydrogel lenses offer an advantage over other materials as to risk of infection with extended wear. The use of prophylactic antibiotics with therapeutic contact lenses in the setting of ocular surface disease remains controversial.

Large-diameter rigid, gas-permeable lenses are beneficial in the treatment of ocular surface disease[90-93] and in atopic keratoconjunctivitis,[94] chronic graft-versus-host disease,[95,96] and Stevens-Johnson syndrome.[97] Although there are no reports specifically on the use of these devices in Sjögren disease, patients with Sjögren disease were included in populations in which benefit was demonstrated.[92,93] There can be confusion as to exactly what a scleral lens or scleral contact lens is, with larger-diameter corneal, corneoscleral, or miniscleral lenses sometimes included in this therapeutic category. Retention of a fluid reservoir over the cornea and lack of corneal touch are key elements to the therapeutic effect of a large-diameter lens, which might also be categorized as a prosthetic device for the ocular surface. Success with therapeutic contact lenses in Sjögren disease requires patience on the part of the fitting clinician and the patient. Trial of many lenses may be required, and this can be a challenge for patients who are uncomfortable at baseline. A well-fitted lens offers nearly immediate improvement in quality of vision and in comfort and can serve to motivate the patient and clinician in the fitting process.

H. Management of Eyelids

For patients with meibomian gland dysfunction, manual expression of the meibomian glands using two cotton-tipped applicators pressed together to compress the eyelid is commonly performed. An alternative method is performed by simultaneous digital pressure on the skin and cotton-tipped applicator pressure on the palpebral conjunctiva so as to compress the gland without risking trauma to the globe.[98] Numerous devices have been developed to aid in the expression of material from the meibomian glands. Warmed gel masks can be applied over the eyelids to help express meibomian gland material, and several different tools have been developed to aid in manual expression. A device recently approved by the FDA, continuous controlled thermal compression (Lipiflow System™), liquefies the meibomian gland secretion and then expresses the material.[99,100] Although this treatment has been noted (observational studies only) to have an extended duration of effect in some cases, further evaluation and controlled comparative clinical trials will be needed to validate the efficacy and cost-effectiveness for such therapy.[101]

When closure or partial closure of the eyelid is indicated for short periods of time, botulinum toxin injection has been used.[102] When other measures fail, surgical options may be needed to manage the eyelid and degree of exposure of the ocular surface. These are summarized in the online supplement to this article (Online Supplement V).

Treatment algorithm based upon severity level and response to therapy

Diagnosis:	Dry Eye Disease		GRADE	
	Aqueous deficiency without meibomian gland disease	Aqueous deficiency with meibomian gland disease	evidence good moderate insufficient	recommendation strong discretionary
Treatment				
Severity Level 1	Education and environment/diet modification	Education and environment/diet modification	good	strong
	Elimination of offending systemic medication	Elimination of offending systemic medication	good	strong
	Artificial tears, gels, ointments	Artificial tears with lipid component	good	strong
		Eyelid therapy: warm compress, massage	good	strong
Severity Level 2 *level 1 therapy inadequate*	Omega 3 essential fatty acid supplement	Omega 3 essential fatty acid supplement	moderate	moderate strong
	Anti-inflammatory therapy: cyclosporine	Anti-inflammatory therapy: cyclosporine	good	moderate strong
	Anti-inflammatory therapy: pulse steroids	Anti-inflammatory therapy: pulse steroids	good	moderate strong
		Topical azithromycin	good	moderate strong
		Liposomal spray	good	moderate strong
		Possible oral doxycycline	good	moderate strong
		Expression of meibomian glands	good	moderate strong
	Punctal plugs	Punctal plugs	good	moderate strong
	Secretagogues	Secretagogues	good	moderate strong
	Moisture chamber spectacles	Moisture chamber spectacles	good	moderate strong
Severity Level 3 *level 2 therapy inadequate*	Topical autologous serum	Topical autologous serum	good	moderate strong
	Contact lenses	Contact lenses	good	moderate strong
	Permanent punctal occlusion	Permanent punctal occlusion	good	moderate strong
		(Lipiflow pulsed thermal compression)	insufficient	discretionary
		(Probing of meibomian gland)	insufficient	discretionary
Severity Level 4 *level 3 therapy inadequate*	Systemic anti-inflammatory medication	Systemic anti-inflammatory medication	moderate	discretionary
	Eyelid surgery	Eyelid surgery	good	moderate strong

[Assumes use of the International Dry Eye Workshop severity scale]

Figure 1. Management algorithm based upon determined level of severity of dry eye disease using the International Dry Eye Workshop severity scale. Progression of therapy is determined by response to prior treatment option. Evidence and strength of recommendation are according to GRADE system.

VI. SUMMARY AND RECOMMENDATIONS

Dry eye disease is one of the most quality-of-life and activity-limiting features of Sjögren disease. In a given patient, the clinician must determine whether the dry eye is due to inadequate production of tears, excess evaporation, or a combination of both mechanisms; success of treatment depends upon proper recognition and approach to therapy.

Evaluation of symptoms can be accomplished by use of a number of questionnaires to grade severity of symptoms. Practical considerations recommend use of three specific questions (Table 2). A number of clinical tests of tear function can be performed in the office setting to quantify the volume and stability of tear function, including tear meniscus height and TFBUT. Determination of tear secretion rate is the most helpful way to differentiate aqueous-deficient dry eye from evaporative dry eye, and this is usually accomplished by the Schirmer test. More advanced diagnosis of dry eye can be achieved by measuring tear film osmolarity, which can also be used to monitor response to therapy. Evaluation of lid blink function and health of the eyelid margin, particularly the meibomian glands, is necessary to quantify evaporative dry eye. Evaluation of the severity of dry eye disease is possible with application of topical dyes, including fluorescein, rose bengal, and lissamine green, to quantify damage to the ocular surface.

Management of dry eye depends upon the nature of the dry eye and the severity of symptoms. The algorithm presented in Figure 1 details the options available. In early disease, tear replacement with topically applied artificial tear or lubricant solutions may be sufficient, but progressive or more severe KCS requires the use of dietary supplements (omega 3 essential fatty acids), anti-inflammatory measures (e.g., topical corticosteroids or cyclosporine), or oral secretagogues. Plugging of the lacrimal puncta can be done once the inflammatory component of dry eye is controlled. Control of lid margin (meibomian gland) disease may require topical antibiotic or systemic doxycycline therapy. The most severe cases of dry eye, particularly those unresponsive to more standard therapy, may require use of topical autologous serum or partial closure of the interpalpebral fissure to reduce surface exposure. Scleral contact lenses may be needed to control severe ocular surface damage.

Dry eye may signal the presence of Sjögren disease, particularly when it is associated with inflammation, difficulty in management, or dry mouth. A patient with suspected Sjögren disease should be referred to a dentist for oral disease prevention/management and to a rheumatologist for systemic treatment.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jtos.2014.12.001.

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