OUTLINE

by all subcommittee members and by the entire Dry Eye WorkShop membership. Comments and suggested revisions were discussed by the subcommittee members and incorporated into the report where deemed appropriate by consensus.

III. ASSESSMENT OF CURRENT DRY EYE THERAPIES

A. Tear Supplementation: Lubricants

1. General Characteristics and Effects

The term "artificial tears" is a misnomer for most products that identify themselves as such, because they do not mimic the composition of human tears. Most function as lubricants, although some more recent formulations mimic the electrolyte composition of human tears (TheraTears® [Advanced Vision Research, Woburn, MA]).[1,2] The ocular lubricants presently available in the United States are approved based on the US Food and Drug Administration (**FDA**) monograph on over-the-counter (**OTC**) products (21 CFR 349) and are not based on clinical efficacy. The monograph specifies permitted active ingredients (eg, demulcents, emulsifiers, surfactants, and viscosity agents) and concentrations, but gives only limited guidance on inactive additives and solution parameters. Certain inactive ingredients that are used in artificial tears sold in the US (eg, castor oil in Endura™ [Allergan, Inc., Irvine, CA] and guar in Systane® [Alcon, Ft Worth, TX]) are not listed in the monograph.

It is difficult to prove that any ingredient in an ocular lubricant acts as an active agent. If there is an active ingredient, it is the polymeric base or viscosity agent, but this has proved difficult to demonstrate. This is either because it is not possible to detect the effects or differences in clinical trials with presently available clinical tests or because the currently available agents do not have any discernable clinical activity beyond a lubrication effect. Although certain artificial tears have demonstrated more success than others in reducing symptoms of irritation or decreasing ocular surface dye staining in head-to-head comparisons, there have been no large scale, masked, comparative clinical trials to evaluate the wide variety of ocular lubricants.

What is the clinical effect of ocular lubricants or artificial tears? Do they lubricate, replace missing tear constituents, reduce elevated tear film osmolarity, dilute or wash out inflammatory or inflammation-inducing agents? Do they, in some instances, actually wash out essential substances found in normal human tears? These questions remain to be answered as more sensitive clinical tests become available to detect changes in the ocular surface.

The foremost objectives in caring for patients with dry eye disease are to improve the patient's ocular comfort and quality of life, and to return the ocular surface and tear film to the normal homeostatic state. Although symptoms can rarely be eliminated, they can often be improved, leading to an improvement in the quality of life. It is more difficult to demonstrate that topical lubricants improve the ocular surface and the tear film abnormalities associated with dry eye. Most clinical studies fail to demonstrate significant correlation between symptoms and clinical test values or between the clinical test values themselves.[3-5] It is not unusual for a dry eye with only mild symptoms to show significant rose bengal staining. Until agents are developed that can restore the ocular surface and tear film to their

normal homeostatic state, the symptoms and signs of dry eye disease will continue.

Ocular lubricants are characterized by hypotonic or isotonic buffered solutions containing electrolytes, surfactants, and various types of viscosity agents. In theory, the ideal artificial lubricant should be preservative-free, contain potassium, bicarbonate, and other electrolytes and have a polymeric system to increase its retention time.[1,6-8] Physical properties should include a neutral to slightly alkaline pH. Osmolarities of artificial tears have been measured to range from about 181 to 354 mOsm/L.[9] 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.

2. Preservatives

The single most critical advance in the treatment of dry eye came with the elimination of preservatives, such as benzalkonium chloride (**BAK**), from OTC lubricants. Because of the risk of contamination of multidose products, most either contain a preservative or employ some mechanism for minimizing contamination. The FDA has required that multidose artificial tears contain preservatives to prevent microbial growth.[10] Preservatives are not required in unit dose vials that are discarded after a single use. The widespread availability of nonpreserved preparations allows patients to administer lubricants more frequently without concern about the toxic effects of preservatives. For patients with moderate-to-severe dry eye disease, the absence of preservatives is of more critical importance than the particular polymeric agent used in ocular lubricants. The ocular surface inflammation associated with dry eye is exacerbated by preserved lubricants; however, nonpreserved solutions are inadequate in themselves to improve the surface inflammation and epithelial pathology seen in dry eye disease.[11]

Benzalkonium chloride is the most frequently used preservative in topical ophthalmic preparations, as well as in topical lubricants. Its epithelial toxic effects have been well established.[12-17] The toxicity of BAK is related to its concentration, the frequency of dosing, the level or amount of tear secretion, and the severity of the ocular surface disease. In the patient with mild dry eye, BAK-preserved drops are usually well tolerated when used 4-6 times a day or less. In patients with moderate-to-severe dry eye, the potential for BAK toxicity is high, due to decreased tear secretion and decreased turnover.[17] Some patients may be using other topical preparations (eg, glaucoma medications) that contain BAK, increasing their exposure to the toxic effects of BAK. Also, the potential for toxicity exists with patient abuse of other OTC products that contain BAK, such as vasoconstrictors.

BAK can damage the corneal and conjunctival epithelium, affecting cell-to-cell junctions and cell shape and microvilli, eventually leading to cell necrosis with sloughing of 1-2 layers of epithelial cells.[17] Preservative-free formulations are absolutely necessary for patients with severe dry eye with ocular surface disease and impairment of lacrimal gland secretion, or for patients on multiple, preserved topical medications for chronic eye disease. Patients with severe dry eye, greatly reduced tear secretion, and punctal occlusion are at particular risk for preservative toxicity. In such patients, the instilled agent cannot be washed out; if this risk has not been appreciated by the clinician, preserved drops might be used at high frequency.

Another additive used in OTC formulations is disodium (**EDTA**). It augments the preservative efficacy of BAK and other preservatives, but, by itself, it is not a sufficient preservative. Used in some nonpreserved solutions, it may help limit microbial growth in opened unit-dose vials. Although use of EDTA may allow a lower concentration of preservative, EDTA may itself be toxic to the ocular surface epithelium. A study comparing two preservative-free solutions, Hypotears PF® (Novartis Ophthalmics, East Hanover, NJ) containing EDTA and Refresh® (Allergan, Inc., Irvine, CA) without EDTA, showed that both formulations had identical safety profiles and were completely nontoxic to the rabbit corneal epithelium.[18] Other studies found that EDTA-containing preparations increased corneal epithelial permeability.[19,20] The potential exists that patients with severe dry eye will find that EDTA-containing preparations increase irritation.

Nonpreserved, single unit-dose tear substitutes are more costly for the manufacturer to produce, more costly for the patients to purchase, and less convenient to use than bottled ocular lubricants. For these reasons, reclosable unit dose vials (eg, Refresh Free [Allergan Inc., Irvine, CA]; Tears Natural Free® [Alcon, Fort Worth, TX]) were introduced. Less toxic preservatives, such as polyquad (polyquaternium-1), sodium chlorite (Purite®), and sodium perborate were developed to allow the use of multidose bottled lubricants and to avoid the known toxicity of BAK-containing solutions.[21,22] The "vanishing" preservatives were sodium perborate and sodium chlorite (TheraTears® [Advanced Vision Research, Woburn, MA], Genteal® [Novartis, East Hanover, NJ], and Refresh Tears® [Allergan Inc., Irvine, CA]).

Sodium chlorite degrades to chloride ions and water upon exposure to UV light after instillation. Sodium perborate is converted to water and oxygen on contact with the tear film. For patients with severe dry eye, even vanishing preservatives may not totally degrade, due to a decrease in tear volume, and may be irritating. Patients prefer bottled preparations for reasons of both cost and ease of use. The ideal lubricant would come in a multidose, easy-to-use bottle that contains a preservative that completely dissipates before reaching the tear film, or is completely nontoxic and nonirritating and maintains absolute sterility with frequent use. One such multi-use, preservative-free product has been introduced to the market (Visine Pure-Tears® [Pfizer, Inc, NJ]).

Ocular ointments and gels are also used in treatment of dry eye disease. Ointments are formulated with a specific mixture of mineral oil and petrolatum. Some contain lanolin,

which can be irritating to the eye and delay corneal wound healing.[23] Individuals with sensitivity to wool may also be sensitive to lanolin.[23] Some ointments contain parabens as preservatives, and these ointments are not well tolerated by patients with severe dry eye. In general, ointments do not support bacterial growth and, therefore, do not require preservatives. Gels containing high molecular weight cross-linked polymers of acrylic acid (carbomers) have longer retention times than artificial tear solutions, but have less visual blurring effect than petrolatum ointments.

3. Electrolyte Composition

Solutions containing electrolytes and or ions have been shown to be beneficial in treating ocular surface damage due to dry eye.[1,6,20,24,25] To date, potassium and bicarbonate seem to be the most critical. Potassium is important to maintain corneal thickness.[7] In a dry-eye rabbit model, a hypotonic tear-matched electrolyte solution (TheraTears® [Advanced Vision Research, Woburn, MA]) increased conjunctival goblet cell density and corneal glycogen content, and reduced tear osmolarity and rose bengal staining after 2 weeks of treatment.[25] The restoration of conjunctival goblet cells seen in the dry-eye rabbit model has been corroborated in patients with dry eye after LASIK.[26]

Bicarbonate-containing solutions promote the recovery of epithelial barrier function in damaged corneal epithelium and aid in maintaining normal epithelial ultrastructure. They may also be important for maintaining the mucin layer of the tear film.[6] Ocular lubricants are available that mimic the electrolyte composition of human tears, eg, TheraTears® (Advanced Vision Research, Woburn, MA) and BION Tears® (Alcon, Fort Worth, TX).[1,2] These also contain bicarbonate, which is critical for forming and maintaining the protective mucin gel in the stomach.[27] Bicarbonate may play a similar role for gel-forming mucins on the ocular surface. Because bicarbonate is converted to carbon dioxide when in contact with air and can diffuse through the plastic unit dose vials, foil packaging of the plastic vials is required to maintain stability.

4. Osmolarity

Tears of patients with dry eye have a higher tear film osmolarity (crystalloid osmolarity) than do those of normal patients.[28,29] Elevated tear film osmolarity causes morphological and biochemical changes to the corneal and conjunctival epithelium[18,30] and is pro-inflammatory.[31] This knowledge influenced the development of hypo-osmotic artificial tears such as Hypotears® (230 mOsm/L [Novartis Ophthalmics, East Hanover, NJ]) and subsequently TheraTears® (181 mOsm/L [Advance Vision Research, Woburn, MA]).[32]

Colloidal osmolality is another factor that varies in artificial tear formulations. While crystalloid osmolarity is related to the presence of ions, colloidal osmolality is dependent largely on macromolecule content. Colloidal osmolarity, also known as *oncotic pressure*, is involved in the control of water transport in tissues. Differences in colloidal osmolality affect the net water flow across membranes, and water flow is eliminated by applying hydrostatic pressure to the downside of the water flow. The magnitude of this osmotic pressure is determined by osmolality differences on the two sides of the membrane. Epithelial cells swell due to damage to their cellular membranes or due to a dysfunction in the pumping mechanism. Following the addition of a fluid with a high colloidal osmolality to the damaged cell surface, deturgescence occurs, leading to a return of normal cell physiology. Theoretically, an artificial tear formulation with a high colloidal osmolality may be of value. Holly and Esquivel evaluated many different artificial tear formulations and showed that Hypotears® (Novartis Ophthalmics, East Hanover, NJ) had the highest colloidal osmolality of all of the formulations tested.[33] Formulations with higher colloidal osmolality have since been marketed (Dwelle® [Dry Eye Company, Silverdale, WA]).

Protection against the adverse effects of increased osmolarity (osmoprotection) has led to development of OTC drops incorporating compatible solutes (such as glycerin, erythritol, and levocarnitine (Optive® [Allergan Inc., Irvine, CA]). It is thought that the compatible solutes distribute between the tears and the intracellular fluids to protect against potential cellular damage from hyperosmolar tears.[34]

5. Viscosity Agents

The stability of the tear film depends on the chemical-physical characteristics of that film interacting with the conjunctival and corneal epithelium via the membrane-spanning mucins (ie, MUC-16 and MUC-4). In the classical three-layered tear film model, the mucin layer is usually thought of as a surfactant or wetting agent, acting to lower the surface tension of the relatively hydrophobic ocular surface, rendering the corneal and conjunctival cells "wettable."[33] Currently, the tear film is probably best described as a hydrated, mucin gel whose mucin concentration decreases with distance from the epithelial cell surface. It may have a protective role similar to that of mucin in the stomach.[35] It may also serve as a "sink" or storage vehicle for substances secreted by the main and accessory lacrimal glands and the ocular surface cells. This may explain why most of the available water-containing lubricants are only minimally effective in restoring the normal homeostasis of the ocular surface. In addition to washing away and diluting out irritating or toxic substances in the tear film, artificial lubricants hydrate gel-forming mucin. While some patients with dry eye have decreased aqueous lacrimal gland secretion, alterations or deficiencies involving mucin also cause dry eye.

Macromolecular complexes added to artificial lubricants act as viscosity agents. The addition of a viscosity agent increases residence time, providing a longer interval of patient comfort. For example, when a viscous, anionic charged carboxymethyl-cellulose (CMC, 100,000 mw) solution was compared with a neutral hydroxymethylcellulose (HPMC) solution, CMC was shown to have a significantly slower rate of clearance from the eye.[36] Viscous agents in active drug

formulations may also prolong ocular surface contact, increasing the duration of action and penetration of the drug.

Viscous agents may also protect the ocular surface epithelium. It is known that rose bengal stains abnormal corneal and conjunctival epithelial cells expressing an altered mucin glycocalyx.[37] Agents such as hydroxymethycellulose (**HMC**), which decrease rose bengal staining in dry eye subjects,[38] may either "coat and protect" the surface epithelium or help restore the protective effect of mucins.

In the US, carboxymethyl cellulose is the most commonly used polymeric viscosity agent (IRI Market Share Data, Chicago, IL), typically in concentrations from 0.25% to 1%, with differences in molecular weight also contributing to final product viscosity. Carboxymethyl cellulose has been found to bind to and be retained by human epithelial cells.[39] Other viscosity agents included in the FDA monograph (in various concentrations) include polyvinyl alcohol, polyethylene glycol, glycol 400, propylene glycol hydroxymethyl cellulose and hydroxypropyl cellulose.

The blurring of vision and esthetic disadvantages of caking and drying on eyelashes are drawbacks of highly viscous agents that patients with mild to moderate dry eye will not tolerate. Lower molecular-weight viscous agents help to minimize these problems. Because patient compliance, comfort, and convenience are important considerations, a range of tear substitute formulations with varying viscosities are needed.

Hydroxypropyl-guar (HP-guar) has been used as a gelling agent in a solution containing glycol 400 and propylene glycol (Systane®, Alcon, Fort Worth, TX). It has been suggested that HP-guar preferentially binds to the more hydrophobic, desiccated or damaged areas of the surface epithelial cells, providing temporary protection for these cells.[40,41] Several commercial preparations containing oil in the form of castor oil (Endura™ [Allergan Inc., Irvine, CA]) or mineral oil (Soothe® [Bausch & Lomb, Rochester, NY]) are purported to aid in restoring or increasing the lipid layer of the tear film.[42,43] Hyaluronic acid is a viscosity agent that has been investigated for years as an "active" compound added to tear substitute formulations for the treatment of dry eye. Hyaluronic acid (0.2%) has significantly longer ocular surface residence times than 0.3 percent HPMC or 1.4 percent polyvinyl alcohol.[44] Some clinical studies reported improvement in [44-48] dry eye in patients treated with sodium hyaluronate-containing solutions compared to other lubricant solutions, whereas others did not.[48] Although lubricant preparations containing sodium hyaluronate have not been approved for use in the US, they are frequently used in some countries.

6. Summary

Although many topical lubricants, with various viscosity agents, may improve symptoms and objective findings, there is no evidence that any agent is superior to another. Most clinical trials involving topical lubricant preparations will document some improvement (but not resolution) of subjective symptoms and improvement in some objective parameters.[4] However, the improvements noted are not necessarily any better than those seen with the vehicle or other nonpreserved artificial lubricants. The elimination of preservatives and the development of newer, less toxic preservatives have made ocular lubricants better tolerated by dry eye patients. However, ocular lubricants, which have been shown to provide some protection of the ocular surface epithelium and some improvement in patient symptoms and objective findings, have not been demonstrated in controlled clinical trials to be sufficient to resolve the ocular surface disorder and inflammation seen in most dry eye sufferers.

B. Tear Retention

1. Punctal Occlusion

a. Rationale

While the concept of permanently occluding the lacrimal puncta with cautery to treat dry eye extends back 70 years,[49] and, although the first dissolvable implants were used 45 years ago,[50] the modern era of punctal plug use began in 1975 with the report by Freeman.[51] Freeman described the use of a dumbbell-shaped silicone plug, which rests on the opening of the punctum and extends into the canaliculus. His report established a concept of punctal occlusion, which opened the field for development of a variety of removable, long-lasting plugs to retard tear clearance in an attempt to treat the ocular surface of patients with deficient aqueous tear production. The Freeman style plug remains the prototype for most styles of punctal plugs.

b. Types

Punctal plugs are divided into two main types: absorbable and nonabsorbable. The former are made of collagen or polymers and last for variable periods of time (3 days to 6 months). The latter nonabsorbable "permanent" plugs include the Freeman style, which consists of a surface collar resting on the punctal opening, a neck, and a wider base. In contrast, the Herrick plug (Lacrimedics [Eastsound,WA]) is shaped like a golf tee and is designed to reside within the canaliculus. It is blue for visualization; other variations are radiopaque. A newly designed cylindrical Smartplug™ (Medennium Inc [Irvine, CA]) expands and increases in diameter in situ following insertion into the canaliculus due to thermodynamic properties of its hydrophilic acrylic composition.

c. Clinical Studies

A variety of clinical studies evaluating the efficacy of punctal plugs have been reported.[52-56] These series generally fall into Level II evidence. Their use has been associated with objective and subjective improvement in patients with both Sjogren and non-Sjogren aqueous tear deficient dry eye, filamentary keratitis, contact lens intolerance, Stevens-Johnson disease, severe trachoma, neurotrophic keratopathy, post-penetrating keratoplasty, diabetic keratopathy, and post-photorefractive keratectomy or laser in situ keratomileusis. Several studies have been performed

to evaluate the effects of punctal plugs on the efficacy of glaucoma medications in reducing intraocular pressure, and these studies have reported conflicting results.[57,58] Beneficial outcome in dry eye symptoms has been reported in 74-86% of patients treated with punctal plugs. Objective indices of improvement reported with the use of punctal plugs include improved corneal staining, prolonged tear film breakup time (**TFBUT**), decrease in tear osmolarity, and increase in goblet cell density. Overall, the clinical utility of punctal plugs in the management of dry eye disease has been well documented.

d. Indications and Contraindications

In a recent review on punctal plugs, it was reported that in a major eye clinic, punctal plugs are considered indicated in patients who are symptomatic of dry eyes, have a Schirmer test (with anesthesia) result less than 5 mm at 5 minutes, and show evidence of ocular surface dye staining.[56]

Contraindications to the use of punctal plugs include allergy to the materials used in the plugs to be implanted, punctal ectropion, and pre-existing nasolacrimal duct obstruction, which would, presumably, negate the need for punctal occlusion. It has been suggested that plugs may be contraindicated in dry eye patients with clinical ocular surface inflammation, because occlusion of tear outflow would prolong contact of the abnormal tears containing proinflammatory cytokines with the ocular surface. Treatment of the ocular surface inflammation prior to plug insertion has been recommended. Acute or chronic infection of the lacrimal canaliculus or lacrimal sac is also a contraindication to use of a plug.

e. Complications

The most common complication of punctal plugs is spontaneous plug extrusion, which is particularly common with the Freeman-style plugs. Over time, an extrusion rate of 50% has been reported, but many of these extrusions took place after extensive periods of plug residence. Most extrusions are of small consequence, except for inconvenience and expense. More troublesome complications include internal migration of a plug, biofilm formation and infection,[59] and pyogenic granuloma formation. Removal of migrated canalicular plugs can be difficult and may require surgery to the nasolacrimal duct system.[60,61]

f. Summary

The extensive literature on the use of punctal plugs in the management of dry eye disease has documented their utility. Several recent reports, however, have suggested that absorption of tears by the nasolacrimal ducts into surrounding tissues and blood vessels may provide a feedback mechanism to the lacrimal gland regulating tear production.[62] In one study, placement of punctal plugs in patients with normal tear production caused a significant decrease in tear production for up to 2 weeks after plug insertion.[63] This cautionary note should be considered when deciding whether to incorporate punctal occlusion into a dry eye disease management plan.

2. Moisture Chamber Spectacles

The wearing of moisture-conserving spectacles has for many years been advocated to alleviate ocular discomfort associated with dry eye. However, the level of evidence supporting its efficacy for dry eye treatment has been relatively limited. Tsubota et al, using a sensitive moisture sensor, reported an increase in periocular humidity in subjects wearing such spectacles.[64] Addition of side panels to the spectacles was shown to further increase the humidity.[65] The clinical efficacy of moisture chamber spectacles has been reported in case reports.[66,67] Kurihashi proposed a related treatment for dry eye patients, in the form of a wet gauze eye mask.[68] Conversely, Nichols et al recently reported in their epidemiologic study that spectacle wearers were twice as likely as emmetropes to report dry eye disease.[69] The reason for this observation was not explained.

There have been several reports with relatively high level of evidence describing the relationship between environmental humidity and dry eye. Korb et al reported that increases in periocular humidity caused a significant increase in thickness of the tear film lipid layer.[70] Dry eye subjects wearing spectacles showed significantly longer interblink intervals than those who did not wear spectacles, and duration of blink (blinking time) was significantly longer in the latter subjects.[70] Instillation of artificial tears caused a significant increase in the interblink interval and a decrease in the blink rate.[71] Maruyama et al reported that dry eye symptoms worsened in soft contact lens wearers when environmental humidity decreased.[72]

3. Contact Lenses

Contact lenses may help to protect and hydrate the corneal surface in severe dry eye conditions. Several different contact lens materials and designs have been evaluated, including silicone rubber lenses and gas permeable scleral-bearing hard contact lenses with or without fenestration.[73-77] Improved visual acuity and comfort, decreased corneal epitheliopathy, and healing of persistent corneal epithelial defects have been reported.[73-77] Highly oxygen-permeable materials enable overnight wear in appropriate circumstances.[75] There is a small risk of corneal vascularization and possible corneal infection associated with the use of contact lenses by dry eye patients.

C. Tear Stimulation: Secretogogues

Several potential topical pharmacologic agents may stimulate aqueous secretion, mucous secretion, or both. The agents currently under investigation by pharmaceutical companies are diquafosol (one of the P2Y2 receptor agonists), rebamipide, gefarnate, ecabet sodium (mucous secretion stimulants), and 15(S)-HETE (MUC1 stimulant). Among them, a diquafosol eye drop has been favorably evaluated in clinical trials. 2% diquafosol (INS365, DE-089 [Santen, Osaka, Japan]; Inspire [Durham, NC]) proved to

be effective in the treatment of dry eye in a randomized, double-masked trial in humans to reduce ocular surface staining.[78] A similar study demonstrated the ocular safety and tolerability of diquafosol in a double-masked, placebo-controlled, randomized study.[79] This agent is capable of stimulating both aqueous and mucous secretion in animals and humans.[80-83] Beneficial effects on corneal epithelial barrier function, as well as increased tear secretion, has been demonstrated in the rat dry eye model.[84] Diquafosol also has been shown to stimulate mucin release from goblet cells in a rabbit dry eye model.[85,86]

The effects of rebamipide (OPC-12759 [Otsuka, Rockville, MD]; Novartis [Basel, Switzerland]) have been evaluated in human clinical trials. In animal studies, rebamipide increased the mucin-like substances on the ocular surface of N-acetylcysteine-treated rabbit eyes.[87] It also had hydroxyl radical scavenging effects on UVB-induced corneal damage in mice.[88]

Ecabet sodium (Senju [Osaka, Japan]; ISTA [Irvine, CA]) is being evaluated in clinical trials internationally, but only limited results have yet been published. A single instillation of ecabet sodium ophthalmic solution elicited a statistically significant increase in tear mucin in dry eye patients.[89] Gefarnate (Santen [Osaka, Japan]) has been evaluated in animal studies. Gefarnate promoted mucin production after conjunctival injury in monkeys.[90] Gefarnate increased PAS-positive cell density in rabbit conjunctiva and stimulated mucin-like glycoprotein stimulation from rat cultured corneal epithelium.[91,92] An in vivo rabbit experiment showed a similar result.[93,94]

The agent 15(S)-HETE, a unique molecule, can stimulate MUC1 mucin expression on ocular surface epithelium.[95]15(S)-HETE protected the cornea in a rabbit model of desiccation-induced injury, probably because of mucin secretion.[96] It has been shown to have beneficial effects on secretion of mucin-like glycoprotein by the rabbit corneal epithelium.[97] Other laboratory studies confirm the stimulatory effect of 15(S)-HETE.[98-101] Some of these agents may become useful clinical therapeutic modalities in the near future.

Two orally administered cholinergic agonists, pilocarpine and cevilemine, have been evaluated in clinical trials for treatment of Sjogren syndrome associated keratoconjunctivitis sicca (**KCS**). Patients who were treated with pilocarpine at a dose of 5 mg QID experienced a significantly greater overall improvement than placebo-treated patients in "ocular problems" in their ability to focus their eyes during reading, and in symptoms of blurred vision compared with placebo-treated patients.[102] The most commonly reported side effect from this medication was excessive sweating, which occurred in over 40% of patients. Two percent of the patients taking pilocarpine withdrew from the study because of drug-related side effects. Other studies have reported efficacy of pilocarpine for ocular signs and symptoms of Sjogren syndrome KCS,[103-105] including an increase in conjunctival goblet cell density after 1 and 2 months of therapy.[106]

Cevilemine is another oral cholinergic agonist that was found to significantly improve symptoms of dryness and aqueous tear production and ocular surface disease compared to placebo when taken in doses of 15 or 30 mg TID.[107,108] This agent may have fewer adverse systemic side effects than oral pilocarpine.

D. Biological Tear Substitutes

Naturally occurring biological, ie, nonpharmaceutical fluids, can be used to substitute for natural tears. The use of serum or saliva for this purpose has been reported in humans. They are usually unpreserved. When of autologous origin, they lack antigenicity and contain various epitheliotrophic factors, such as growth factors, neurotrophins, vitamins, immunoglobulins, and extracellular matrix proteins involved in ocular surface maintenance. Biological tear substitutes maintain the morphology and support the proliferation of primary human corneal epithelial cells better than pharmaceutical tear substitutes.[109] However, despite biomechanical and biochemical similarities, relevant compositional differences compared with normal tears exist and are of clinical relevance.[110] Additional practical problems concern sterility and stability, and a labor-intensive production process or a surgical procedure (saliva) is required to provide the natural tear substitute to the ocular surface.

1. Serum

Serum is the fluid component of full blood that remains after clotting. Its topical use for ocular surface disease was much stimulated by Tsubota's prolific work in the late 1990s.[111] The practicalities and published evidence of autologous serum application were recently reviewed.[112] The use of blood and its components as a pharmaceutical preparation in many countries is restricted by specific national laws. To produce serum eye drops and to use them for outpatients, a license by an appropriate national body may be required in certain countries. The protocol used for the production of serum eye drops determines their composition and efficacy. An optimized protocol for the production was recently published.[113] Concentrations between 20% and 100% of serum have been used. The efficacy seems to be dose-dependent.

Because of significant variations in patient populations, production and storage regimens, and treatment protocols, the efficacy of serum eye drops in dry eyes has varied substantially between studies.[113] Three published prospective randomized studies with similar patient populations (predominantly immune disease associated dry eye, ie, Sjogren syndrome) are available. When comparing 20% serum with 0.9% saline applied 6 times per day, Tananuvat et al found only a trend toward improvement of symptoms and signs of dry eyes,[114] whereas Kojima et al reported significant improvement of symptom scores, fluorescein-breakup time (**FBUT**), and fluorescein and rose bengal staining.[115]

A prospective clinical cross-over trial compared 50% serum eyedrops against the commercial lubricant previously

used by each patient. Symptoms improved in 10 out 16 patients, and impression cytological findings improved in 12 out of 25 eyes.[116] Noda-Tsuruya and colleagues found that 20% autologous serum significantly improved TFBUT and decreased conjunctival rose bengal and cornea fluorescein staining 1-3 months postoperatively, compared to treatment with artificial tears, which did not change these parameters.[117] Additional reports of successful treatment of persistent epithelial defects—where success is more clearly defined as "healing of the defect"—with autologous serum substantiate the impression that this is a valuable therapeutic option for ocular surface disease.[118]

2. Salivary Gland Autotransplantation

Salivary submandibular gland transplantation is capable of replacing deficient mucin and the aqueous tear film phase. This procedure requires collaboration between an ophthalmologist and a maxillofacial surgeon. With appropriate microvascular anastomosis, 80% of grafts survive. In patients with absolute aqueous tear deficiency, viable submandibular gland grafts, in the long-term, provide significant improvement of Schirmer test FBUT, and rose bengal staining, as well as reduction of discomfort and the need for pharmaceutical tear substitutes. Due to the hypo-osmolarity of saliva, compared to tears, excessive salivary tearing can induce a microcystic corneal edema, which is temporary, but can lead to epithelial defects.[110] Hence, this operation is indicated only in end-stage dry eye disease with an absolute aqueous tear deficiency (Schirmer-test wetting of 1 mm or less), a conjunctivalized surface epithelium, and persistent severe pain despite punctal occlusion and at least hourly application of unpreserved tear substitutes. For this group of patients, such surgery is capable of substantially reducing discomfort, but often has no effect on vision.[119,120]

E. Anti-Inflammatory Therapy

Disease or dysfunction of the tear secretory glands leads to changes in tear composition, such as hyperosmolarity, that stimulate the production of inflammatory mediators on the ocular surface.[31,121] Inflammation may, in turn, cause dysfunction or disappearance of cells responsible for tear secretion or retention.[122] Inflammation can also be initiated by chronic irritative stress (eg, contact lenses) and systemic inflammatory/autoimmune disease (eg, rheumatoid arthritis). Regardless of the initiating cause, a vicious circle of inflammation can develop on the ocular surface in dry eye that leads to ocular surface disease. Based on the concept that inflammation is a key component of the pathogenesis of dry eye, the efficacy of a number of anti-inflammatory agents for treatment of dry eye disease has been evaluated in clinical trials and animal models.

1. Cyclosporine

The potential of cyclosporine-A (**CsA**) for treating dry eye disease was initially recognized in dogs that develop spontaneous KCS.[123] The therapeutic efficacy of CsA for human KCS was then documented in several small, single-center, randomized, double-masked clinical trials.[124,125] CsA emulsion for treatment of KCS was subsequently evaluated in several large multicenter, randomized, double-masked clinical trials.

In a Phase 2 clinical trial, four concentrations of CsA (0.05%, 0.1%, 0.2%, or 0.4%) administered twice daily to both eyes of 129 patients for 12 weeks was compared to vehicle treatment of 33 patients.[126] CsA was found to significantly decrease conjunctival rose bengal staining, superficial punctate keratitis, and ocular irritation symptoms (sandy or gritty feeling, dryness, and itching) in a subset of 90 patients with moderate-to-severe KCS. There was no clear dose response; CsA 0.1% produced the most consistent improvement in objective endpoints, whereas CsA 0.05% gave the most consistent improvement in patient symptoms (Level I).

Two independent Phase 3 clinical trials compared twice-daily treatment with 0.05% or 0.1% CsA or vehicle in 877 patients with moderate-to-severe dry eye disease.[127] When the results of the two Phase 3 trials were combined for statistical analysis, patients treated with CsA, 0.05% or 0.1%, showed significantly ($P < 0.05$) greater improvement in two objective signs of dry eye disease (corneal fluorescein staining and anesthetized Schirmer test values) compared to those treated with vehicle. An increased Schirmer test score was observed in 59% of patients treated with CsA, with 15% of patients having an increase of 10 mm or more. In contrast, only 4% of vehicle-treated patients had this magnitude of change in their Schirmer test scores ($P < 0.0001$).

CsA 0.05% treatment also produced significantly greater improvements ($P < 0.05$) in three subjective measures of dry eye disease (blurred vision symptoms, need for concomitant artificial tears, and the global response to treatment). No dose-response effect was noted. Both doses of CSA exhibited an excellent safety profile with no significant systemic or ocular adverse events, except for transient burning symptoms after instillation in 17% of patients. Burning was reported in 7% of patients receiving the vehicle. No CsA was detected in the blood of patients treated with topical CsA for 12 months. Clinical improvement from CsA that was observed in these trials was accompanied by improvement in other disease parameters. Treated eyes had an approximately 200% increase in conjunctival goblet cell density.[128] Furthermore, there was decreased expression of immune activation markers (ie, HLA-DR), apoptosis markers (ie, Fas), and the inflammatory cytokine IL-6 by the conjunctival epithelial cells.[129,130] The numbers of CD3-, CD4-, and CD8-positive T lymphocytes in the conjunctiva decreased in cyclosporine-treated eyes, whereas vehicle-treated eyes showed an increased number of cells expressing these markers.[131] After treatment with 0.05% cyclosporine, there was a significant decrease in the number of cells expressing the lymphocyte activation markers CD11a and HLA-DR, indicating less activation of lymphocytes compared with vehicle-treated eyes.

Two additional immunophilins, pimecrolimus and tacrolimus, have been evaluated in clinical trials of KCS.

2. Corticosteroids

a. Clinical Studies

Corticosteroids are an effective anti-inflammatory therapy in dry eye disease. Level I evidence is published for a number of corticosteroid formulations. In a 4-week, double-masked, randomized study in 64 patients with KCS and delayed tear clearance, loteprednol etabonate 0.5% ophthalmic suspension (Lotemax [Bausch and Lomb, Rochester, NY]), q.i.d., was found to be more effective than its vehicle in improving some signs and symptoms.[132]

In a 4-week, open-label, randomized study in 32 patients with KCS, patients receiving fluorometholone plus artificial tear substitutes (**ATS**) experienced lower symptom severity scores and lower fluorescein and rose bengal staining than patients receiving either ATS alone or ATS plus flurbiprofen.[133]

A prospective, randomized clinical trial compared the severity of ocular irritation symptoms and corneal fluorescein staining in two groups of patients, one treated with topical nonpreserved methylprednisolone for 2 weeks, followed by punctal occlusion (Group 1), with a group that received punctal occlusion alone (Group 2).[134] After 2 months, 80% of patients in Group 1 and 33% of patients in Group 2 had complete relief of ocular irritation symptoms. Corneal fluorescein staining was negative in 80% of eyes in Group 1 and 60% of eyes in Group 2 after 2 months. No steroid-related complications were observed in this study.

Level III evidence is also available to support the efficacy of corticosteroids. In an open-label, non-comparative trial, extemporaneously formulated nonpreserved methylprednisolone 1% ophthalmic suspension was found to be clinically effective in 21 patients with Sjogren syndrome KCS.[135] In a review, it was stated that "...clinical improvement of KCS has been observed after therapy with anti-inflammatory agents, including corticosteroids."[136]

In the US Federal Regulations, ocular corticosteroids receiving "class labeling" are indicated for the treatment "...of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation." We interpret that KCS is included in this list of steroid-responsive inflammatory conditions.[137-140]

b. Basic Research

Corticosteroids are the standard anti-inflammatory agent for numerous basic research studies of inflammation, including the types that are involved in KCS. The corticosteroid methylprednisolone was noted to preserve corneal epithelial smoothness and barrier function in an experimental murine model of dry eye.[141] This was attributed to its ability to maintain the integrity of corneal epithelial tight junctions and decrease desquamation of apical corneal epithelial cells.[142] A concurrent study showed that methylprednislone prevented an increase in MMP-9 protein in the corneal epithelium, as well as gelatinase activity in the corneal epithelium and tears in response to experimental dry eye.[141]

Preparations of topically applied androgen and estrogen steroid hormones are currently being evaluated in randomized clinical trials. A trial of topically applied 0.03% testosterone was reported to increase the percentage of patients that had meibomian gland secretions with normal viscosity and to relieve discomfort symptoms after 6 months of treatment compared to vehicle.[143] TFBUT and lipid layer thickness were observed to increase in a patient with KCS who was treated with topical androgen for 3 months.[144] Tear production and ocular irritation symptoms were reported to increase following treatment with topical 17 beta-oestradiol solution for 4 months.[145]

3. Tetracyclines

a. Properties of Tetracyclines and Their Derivatives

1) Antibacterial Properties

The antimicrobial effect of oral tetracycline treatment analogues (eg, minocycline, doxycline) has previously been discussed by Shine et al,[146] Dougherty et al,[147] and Ta et al.[148] It is hypothesized that a decrease in bacterial flora producing lipolytic exoenzymes[146,148] and inhibition of lipase production[147] with resultant decrease in meibomian lipid breakdown products[146] may contribute to improvement in clinical parameters in dry eye-associated diseases.

2) Anti-Inflammatory Properties

The tetracyclines have anti-inflammatory as well as antibacterial properties that may make them useful for the management of chronic inflammatory diseases. These agents decrease the activity of collagenase, phospholipase A2, and several matrix metalloproteinases, and they decrease the production of interleukin (**IL**)-1 and tumor necrosis factor (**TNF**)-alpha in a wide range of tissues, including the corneal epithelium.[149-151] At high concentrations, tetracyclines inhibit staphylococcal exotoxin-induced cytokines and chemokines.[152,153]

3) Anti-angiogenic Properties

Angiogenesis, the formation of new blood vessels, occurs in many diseases. These include benign conditions (eg, rosacea) and malignant processes (eg, cancer). Minocycline and doxycycline inhibit angiogenesis induced by implanted tumors in rabbit cornea.[154] The anti-angiogenic effect of tetracycline may have therapeutic implications in inflammatory processes accompanied by new blood vessel formation. Well-controlled studies must be performed, at both the laboratory and clinical levels, to investigate this potential.[155]

b. Clinical Applications of Tetracycline

1) Acne Rosacea

Rosacea, including its ocular manifestations, is an inflammatory disorder, occurring mainly in adults, with peak severity in the third and fourth decades. Current recom-

mendations are to treat rosacea with long-term doxycycline, minocycline, tetracycline, or erythromycin.[156] These recommendations may be tempered by certain recent reports that in women, the risk of developing breast cancer and of breast cancer morbidity increases cumulatively with duration of antibiotic use, including tetracyclines.[157,158] Another large study did not substantiate these findings.[159]

Tetracyclines and their analogues are effective in the treatment of ocular rosacea,[160,161] for which a single daily dose of doxycycline may be effective.[162] In addition to the anti-inflammatory effects of tetracyclines, their ability to inhibit angiogenesis may contribute to their effectiveness in rosacea-related disorders. Factors that promote angiogenesis include protease-triggered release of angiogenic factors stored in the extracellular matrix, inactivation of endothelial growth factor inhibitors, and release of angiogenic factors from activated macrophages.[155,163]

Tetracyclines are also known to inhibit matrix metalloproteinase expression, suggesting a rationale for their use in ocular rosacea.[164] Although tetracyclines have been used for management of this disease, no randomized, placebo-controlled, clinical trials have been performed to assess their efficacy.[153]

2) Chronic Posterior Blepharitis: Meibomianitis, Meibomian Gland Dysfunction

Chronic blepharitis is typically characterized by inflammation of the eyelids. There are multiple forms of chronic blepharitis, including staphylococcal, seborrheic (alone, mixed seborrheic/staphylococcal, seborrheic with meibomian seborrhea, seborrheic with secondary meibomitis), primary meibomitis, and others, like atopic, psoriatic, and fungal infections.[165] Meibomian gland dysfunction (**MGD**) has been associated with apparent aqueous-deficient dry eye. Use of tetracycline in patients with meibomianitis has been shown to decrease lipase production by tetracycline-sensitive as well as resistant strains of staphylococci. This decrease in lipase production was associated with clinical improvement.[147] Similarly, minocycline has been shown to decrease the production of diglycerides and free fatty acids in meibomian secretions. This may be due to lipase inhibition by the antibiotic or a direct effect on the ocular flora.[146] One randomized, controlled clinical trial of tetracycline in ocular rosacea compared symptom improvement in 24 patients treated with either tetracycline or doxycycline.[166] All but one patient reported an improvement in symptoms after 6 weeks of therapy. No placebo group was included in this trial.

A prospective, randomized, double-blind, placebo-controlled, partial crossover trial compared the effect of oxytetracycline to provide symptomatic relief of blepharitis with or without rosacea. Only 25% of the patients with blepharitis without rosacea responded to the antibiotic, whereas 50% responded when both diseases were present.[167] In another trial of 10 patients with both acne rosacea and concomitant meibomianitis, acne rosacea without concomitant ocular involvement, or seborrheic blepharitis, minocycline 50 mg daily for 2 weeks followed by 100 mg daily for a total of 3 months significantly decreased bacterial flora ($P = 0.0013$). Clinical improvement was seen in all patients with meibomianitis.[148]

Because of the improvement observed in small clinical trials of patients with meibomianitis, the American Academy of Ophthalmology recommends the chronic use of either doxycycline or tetracycline for the management of meibomianitis.[165] Larger randomized placebo-controlled trials assessing symptom improvement rather than surrogate markers are needed to clarify the role of this antibiotic in blepharitis treatment.[153] Tetracycline derivatives (eg, minocycline, doxycycline) have been recommended as treatment options for chronic blepharitis because of their high concentration in tissues, low renal clearance, long half-life, high level of binding to serum proteins, and decreased risk of photosensitization.[168]

Several studies have described the beneficial effects of minocycline and other tetracycline derivatives (eg, doxycycline) in the treatment of chronic blepharitis.[146,147,168,169] Studies have shown significant changes in the aqueous tear parameters, such as tear volume and tear flow, following treatment with tetracycline derivatives (eg, minocycline). One study also demonstrated a decrease in aqueous tear production that occurred along with clinical improvement.[170]

A recently published randomized, prospective study by Yoo Se et al compared different doxycycline doses in 150 patients (300 eyes) who had chronic meibomian gland dysfunction and who did not respond to lid hygiene and topical therapy for more than 2 months.[171] All topical therapy was stopped for at least 2 weeks prior to beginning the study. After determining the TFBUT and Schirmer test scores, patients were divided into three groups: a high dose group (doxycycline, 200 mg, twice a day), a low dose group (doxycycline, 20 mg, twice a day) and a control group (placebo). After one month, TFBUT, Schirmer scores, and symptoms improved. Both the high- and low-dose groups had statistically significant improvement in TFBUT after treatment. This implies that low-dose doxycycline (20 mg twice a day) therapy may be effective in patients with chronic meibomian gland dysfunction.

3) Dosage and Safety

Systemic administration of tetracyclines is widely recognized for the ability to suppress inflammation and improve symptoms of meibomianitis.[172,173] The optimal dosing schedule has not been established; however, a variety of dose regimens have been proposed including 50 or 100 mg doxycycline once a day,[174] or an initial dose of 50 mg a day for the first 2 weeks followed by 100 mg a day for a period of 2.5 months, in an intermittent fashion.[146-148,170] Others have proposed use of a low dose of doxycycline (20 mg) for treatment of chronic blepharitis on a long-term basis.[171] The safety issues associated with long-term oral tetracycline therapy, including minocycline, are well known. Many management approaches have been suggested for the use of tetracycline and its derivatives; however, a safe but adequate option in management needs to be considered because of

Table 2. Dry eye severity grading scheme

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic occurs under environ stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity limiting episodic	Annoying, chronic and/or constant limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/–	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤ 10	≤ 5	Immediate
Schirmer score (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2

*Must have signs AND symptoms. TBUT: fluorescein tear break-up time. MGD: meibomian gland disease

Reprinted with permission from Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome. A Delphi approach to treatment recommendations. *Cornea* 2006;25:90-7

the new information regarding the potentially hazardous effects of prolonged use of oral antibiotics. A recent study suggested that a 3-month course of 100 mg of minocycline might be sufficient to bring significant meibomianitis under control, as continued control was maintained for at least 3 months after cessation of therapy.[170]

In an experimental murine model of dry eye, topically applied doxycycline was found to preserve corneal epithelial smoothness and barrier function.[141] It also preserved the integrity of corneal epithelial tight junctions in dry eyes, leading to a marked decrease in apical corneal epithelial cell desquamation.[142] This corresponded to a decrease in MMP-9 protein in the corneal epithelium and reduced gelatinase activity in the corneal epithelium and tears.[141]

F. Essential Fatty Acids

Essential fatty acids are necessary for complete health. They cannot be synthesized by vertebrates and must be obtained from dietary sources. Among the essential fatty acids are 18 carbon omega-6 and omega-3 fatty acids. In the typical western diet, 20-25 times more omega-6 than omega-3 fatty acids are consumed. Omega-6 fatty acids are precursors for arachidonic acid and certain proinflammatory lipid mediators (PGE2 and LTB4). In contrast, certain omega-3 fatty acids (eg, EPA found in fish oil) inhibit the synthesis of these lipid mediators and block production of IL-1 and TNF-alpha.[175,176]

A beneficial clinical effect of fish oil omega-3 fatty acids on rheumatoid arthritis has been observed in several double-masked, placebo-controlled clinical trials.[177,178] In a prospective, placebo-controlled clinical trial of the essential fatty acids, linoleic acid and gamma-linolenic acid administered orally twice daily produced significant improvement in ocular irritation symptoms and ocular surface lissamine green staining.[179] Decreased conjunctival HLA-DR staining also was observed.

G. Environmental Strategies

Factors that may decrease tear production or increase tear evaporation, such as the use of systemic anticholinergic medications (eg, antihistamines and antidepressants) and desiccating environmental stresses (eg, low humidity and air conditioning drafts) should be minimized or eliminated.[180-182] Video display terminals should be lowered below eye level to decrease the interpalpebral aperture, and patients should be encouraged to take periodic breaks with eye closure when reading or working on a computer.[183] A humidified environment is recommended to reduce tear evaporation. This is particularly beneficial in dry climates and high altitudes. Nocturnal lagophthalmos can be treated by wearing swim goggles, taping the eyelid closed, or tarsorrhapy.

IV. TREATMENT RECOMMENDATIONS

In addition to material presented above, the subcommittee members reviewed the Dry Eye Preferred Practice Patterns of the American Academy of Ophthalmology and the International Task Force (ITF) Delphi Panel on dry

Table 3. Dry eye menu of treatments

Artificial tears substitutes
Gels/Ointments
Moisture chamber spectacles
Anti-inflammatory agents (topical CsA and corticosteroids, omega-3 fatty acids)
Tetracyclines
Plugs
Secretogogues
Serum
Contact lenses
Systemic immunosuppressives
Surgery (AMT, lid surgery, tarsorrhaphy, MM & SG transplant)

AMT = amniotic membrane transplantation; MM = mucous membrane; SG = salivary gland

Table 4. Treatment recommendations by severity level

Level 1:
Education and environmental/dietary modifications
Elimination of offending systemic medications
Artificial tear substitutes, gels/ointments
Eye lid therapy

Level 2:
If Level 1 treatments are inadequate, add:
Anti-inflammatories
Tetracyclines (for meibomianitis, rosacea)
Punctal plugs
Secretogogues
Moisture chamber spectacles

Level 3:
If Level 2 treatments are inadequate, add:
Serum
Contact lenses
Permanent punctal occlusion

Level 4:
If Level 3 treatments are inadequate, add:
Systemic anti-inflammatory agents
Surgery (lid surgery, tarsorrhaphy; mucus membrane, salivary gland, amniotic membrane transplantation)

Modified from: International Task Force Guidelines for Dry Eye[185]

eye treatment prior to formulating their treatment guidelines.[184,185] The group favored the approach taken by the ITF, which based treatment recommendations on disease severity. A modification of the ITF severity grading scheme that contains 4 levels of disease severity based on signs and symptoms was formulated (Table 2). The subcommittee members chose treatments for each severity level from a menu of therapies for which evidence of therapeutic effect has been presented (Table 3). The treatment recommendations by severity level are presented in Table 4. It should be noted that these recommendations may be modified by practitioners based on individual patient profiles and clinical experience. The therapeutic recommendations for level 4 severity disease include surgical modalities to treat or prevent sight-threatening corneal complications. Discussion of these therapies is beyond the scope of this report.

V. UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

There have been tremendous advances in the treatment of dry eye and ocular surface disease in the last two decades, including FDA approval of cyclosporin emulsion as the first therapeutic agent for treatment of KCS in the United States. There has been a commensurate increase in knowledge regarding the pathophysiology of dry eye. This has led to a paradigm shift in dry eye management from simply lubricating and hydrating the ocular surface with artificial tears to strategies that stimulate natural production of tear constituents, maintain ocular surface epithelial health and barrier function, and inhibit the inflammatory factors that adversely impact the ability of ocular surface and glandular epithelia to produce tears. Preliminary experience using this new therapeutic approach suggests that quality of life can be improved for many patients with dry eye and that initiating these strategies early in the course of the disease may prevent potentially blinding complications of dry eye. It is likely that future therapies will focus on replacing specific tear factors that have an essential role in maintaining ocular surface homeostasis or inhibiting key inflammatory mediators that cause death or dysfunction of tear secreting cells. This will require additional research to identify these key factors and better diagnostic tests to accurately measure their concentrations in minute tear fluid samples. Furthermore, certain disease parameters may be identified that will identify whether a patient has a high probability of responding to a particular therapy. Based on the progress that has been made and the number of therapies in the pipeline, the future of dry eye therapy seems bright.

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(Parenthetical codes following references indicate level of evidence, as described in Table 1. CS = Clinical Study; BS = Basic Science.)

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EXHIBIT E

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Topical Cyclosporine 0.05% for the Prevention of Dry Eye Disease Progression

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Abstract

Purpose: To assess the prognosis of dry eye in patients treated with cyclosporine 0.05% or artificial tears by using the International Task Force (ITF) guidelines.
Methods: This was a single-center, investigator-masked, prospective, randomized, longitudinal trial. Dry eye patients received twice-daily treatment with either cyclosporine 0.05% (Restasis®; Allergan, Inc., Irvine, CA; $n = 36$) or artificial tears (Refresh Endura®; Allergan, Inc., Irvine, CA; $n = 22$) for 12 months. Disease severity was determined at baseline and month 12 according to the consensus guidelines developed by the ITF. Dry eye signs and symptoms were evaluated at baseline and months 4, 8, and 12.
Results: Baseline sign and symptom scores and the proportion of patients with the disease severity level 2 or 3 were comparable in both groups ($P > 0.05$). At month 12, 34 of 36 cyclosporine patients (94%) and 15 of 22 artificial tear patients (68%) experienced improvements or no change in their disease severity ($P = 0.007$) while 2 of 36 cyclosporine patients (6%) and 7 of 22 artificial tears patients (32%) had disease progression ($P < 0.01$). Cyclosporine 0.05% improved Schirmer test scores, tear breakup time, and Ocular Surface Disease Index scores throughout the study, with significant ($P < 0.01$) differences compared with artificial tears being observed at months 8 and 12.
Conclusions: Treatment with cyclosporine 0.05% may slow or prevent disease progression in patients with dry eye at severity levels 2 or 3.

Introduction

Patients with dry eye disease suffer from ocular irritation often accompanied by vision impairment, which limits important daily activities and negatively impacts quality of life (QoL).[1–3] The prevalence of dry eye disease is estimated to be from 5% to >30%.[4,5] The largest US cross-sectional survey studies, the Women's Health Study (WHS) and the Physician Health Study (PHS), indicated that the prevalence of dry eye disease among women and men aged over 50 years is 7.8% and 4.3%, respectively. Using this prevalence data, ~4.9 million Americans aged over 50 years are estimated to be affected by dry eye disease.[6,7]

The diagnosis and treatment of dry eye is challenging.[8] The Wilmer Eye Institute at Johns Hopkins University recently invited the International Task Force (ITF) of 17 dry eye experts to create guidelines for the diagnosis and treatment of dry eye disease by using a Delphi consensus technique.[9] The ITF panel categorized dry eye disease severity into 4 levels (Table 1), with increasing severity from 1 to 4, and developed consensus treatment guidelines. The level of disease severity was considered the most important factor in determining the appropriate range of therapeutic options.[9] While counseling, education, and preserved artificial tears were recommended for the management of patients diagnosed at severity level 1, unpreserved artificial tears, topical cyclosporine, and/or corticosteroids were recommended for patients at severity level 2. Punctal plugs, oral tetracyclines, systemic immunomodulators, and surgery were reserved for the management of dry eye patients diagnosed at severity levels 3 and 4.[9]

A key recommendation of the ITF panel was the use of topical anti-inflammatory therapy in patients with clinically apparent ocular surface inflammation.[9] This recommendation stemmed from the recent evidence indicating that inflammation plays a major role in the disease etiology and may be a unifying mechanism that underlies dry eye

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TABLE 1. CRITERIA USED TO DETERMINE THE LEVELS OF DRY EYE SEVERITY ACCORDING TO ITF GUIDELINES[8]

	Symptoms	*Signs*	*Staining*
Level 1	Mild to moderate	Mild/moderate conjunctival signs	None
Level 2	Moderate to severe	Tear film signs, visual signs	Mild punctate corneal and conjunctival staining
Level 3	Severe	Corneal filamentary keratitis	Central corneal staining
Level 4	Severe	Corneal erosions, conjunctival scarring	Severe corneal staining

Disease severity is categorized into 4 levels based on the severity of symptoms and signs. At least one sign and one symptom of each category should be present to qualify for the corresponding level assignment.

disease.[10–12] Therefore, it was suggested that the chronic use of safe anti-inflammatory therapies that normalize tear film composition early in the disease process may have the potential to slow, prevent, or reverse dry eye progression.[13]

Ophthalmic cyclosporine 0.05% emulsion (Restasis®; Allergan, Inc., Irvine, CA) is the only anti-inflammatory medication approved by the Food and Drug Administration to increase tear production in dry eye patients.[14] In T lymphocytes, cyclosporine binds to cyclophilin A and inhibits calcineurin-catalyzed dephosphorylation of the nuclear factor for T-cell activation.[15,16] Cyclosporine thereby inhibits IL-2 transcription, which upon secretion stimulates T-cell division by a self-propagating autocrine and paracrine loop.[16] In humans, topical administration of cyclosporine 0.05% has been shown to decrease the number of activated T cells and expression of inflammatory markers in the conjunctiva of dry eye patients.[17,18] These findings suggest that topical cyclosporine 0.05% targets the underlying inflammatory processes in dry eye disease. Therefore, chronic treatment with cyclosporine 0.05% may offer the potential to alter the course of dry eye disease.

Wilson and Stulting recently evaluated the clinical applicability of the ITF guidelines.[13] Physicians participating in that study successfully implemented the ITF guidelines for diagnosis and treatment of dry eye patients.[13] Using the ITF guidelines, this study was designed to assess the prognosis of dry eye disease in patients treated with cyclosporine 0.05% or artificial tears.

Methods

Study design

This was a single-center, investigator-masked, randomized, prospective, longitudinal clinical trial. The study was approved by the Western institutional review board in Olympia, WA, and was registered with ClinicalTrials.gov (identifier # NCT00567983). Inclusion criteria were of age 18 years or older, diagnosis of dry eye without lid margin disease or altered tear distribution and clearance, and a disease severity of level 2 or 3 as defined by the ITF guidelines (Table 1).[9] Primary exclusion criteria were prior use of topical cyclosporine 0.05% within the last year, topical or systemic use of anti-inflammatory or anti-allergy medications, active ocular infection or inflammatory disease, or uncontrolled systemic disease that can exacerbate dry eye disease. Patients who wore contact lenses were also excluded from the study. All participating patients signed a written consent form before initiation of the study-specific procedures.

Patients were randomly assigned in a 3:2 ratio to twice-daily treatment with either cyclosporine 0.05% or artificial tears (Refresh Endura®; Allergan, Inc., Irvine, CA) in both eyes for 12 months. The randomization ratio was an empirical estimation due to lack of adequate epidemiological information to conduct power calculations prior to initiating the study. Randomization was performed by a statistical program and was overseen by the research coordinator. Patients were enrolled in the study and initiated therapy after screening and randomization on the same day at the baseline visit (month 0). All patients were allowed to utilize rescue artificial tears as needed if discomfort was experienced. The primary objective of this study was to assess the potential of topical cyclosporine 0.05% therapy to halt or slow disease progression relative to control at month 12 based on the ITF severity categorization (Table 1). The secondary outcome variables were the changes in dry eye signs and symptoms. The study was conducted in compliance with regulations of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

Disease severity and dry eye signs and symptoms

Disease severity was assessed according to the ITF consensus guidelines at baseline and month 12 (Table 1).[9] Patients were evaluated for signs and symptoms of dry eye by Schirmer test with anesthesia, tear breakup time (TBUT), ocular surface staining, and Ocular Surface Disease Index (OSDI) at baseline (month 0) and after receiving the study treatments at months 4, 8, and 12. In each study visit, TBUT was evaluated first, followed by ocular surface staining and Schirmer test, respectively. The TBUT was measured using fluorescein dye. Ocular surface damage was assessed by the Oxford method using sodium fluorescein to stain the cornea and lissamine green to stain the nasal and temporal bulbar conjunctiva.[19] The scoring scale for ocular staining was 0 to 5 in cornea, 0 to 5 in temporal conjunctiva, and 0 to 5 in nasal conjunctiva, with 0 representing no staining and 5 representing severe staining. These individual scores were then summed for the total Oxford score, which ranged from 0 to 15. The change from baseline was calculated by subtracting the baseline score from the months 4, 8, and 12 scores. The symptoms of ocular irritation and their impact on visual functioning was assessed by OSDI, a validated 12-item questionnaire, on a scale of 0 to 100 with 0 representing asymptomatic and 100 representing severe debilitating dry eye disease.[20]

Goblet cell density

The density of goblet cells in bulbar conjunctiva was evaluated at baseline and month 12. Impression cytology was performed in both eyes after evaluation of TBUT, ocular staining, and Schirmer test. Goblet cells were collected on cellulose acetate filters (HAWP 304 FO; Millipore Corp., Billerica, MA). The filters were fixated in glacial acetic acid, formaldehyde, and 70% ethanol and subsequently stained with a modified periodic acid–Schiff Papanicolaou stain. Goblet cells were counted in 5 (400 × 400 mm) representative microscopic fields on each filter.[21]

Statistical analyses

Patients who completed 12 months of treatment were included in the analyses. The results were presented as mean ± SD. Intergroup comparisons of categorical variables were performed using the chi-square or Fisher's exact test. Continuous variables were analyzed using nonparametric tests (Mann–Whitney tests for between-group comparisons and Wilcoxon signed rank tests for within-group comparisons). A P value < 0.05 was considered a statistically significant difference. Statview software (SAS Institute, Cary, NC) was used for all analyses.

Results

Patient disposition and disease characteristics

Of 74 patients enrolled between February 2006 and January 2007, 58 patients completed the 12-month study and were included in the analyses (Table 2). Forty-one patients were female and 17 patients were male. The distribution of patients with disease severity of level 2 or 3 was similar in both treatment groups at baseline. Approximately two-thirds of dry eye patients in both groups were diagnosed at severity level 2, while one-third of patients was diagnosed at severity level 3 (Table 2). There were no significant between-group differences in the mean age ($P = 0.667$) or distribution of gender ($P = 0.800$).

Sixteen patients discontinued the study. The number of discontinuations was significantly higher among patients treated with artificial tears compared with those treated with cyclosporine 0.05% (11 vs. 5; $P = 0.028$; Table 2). Of 11 discontinuations in the artificial tear group, 9 patients discontinued the study because of discomfort upon instillation, and 2 patients were lost to follow-up or moved. Seven of these patients had a disease severity of level 2, and 4 patients had a disease severity of level 3. Of the 5 discontinuations in the cyclosporine group, 2 patients discontinued the study because of discomfort upon instillation while 3 were lost to follow-up or moved. Three of these patients had a disease severity of level 2, and 2 patients had a disease severity of level 3.

Disease severity

At month 12, significantly more patients treated with artificial tears had more severe signs and symptoms of disease than did those treated with cyclosporine 0.05% and, therefore, were categorized as progressing to a higher disease severity level (7 of 22 [32%] patients vs. 2 of 36 [6%], respectively; $P < 0.007$; Fig. 1). In contrast, a greater percentage of patients treated with cyclosporine 0.05% had less severe signs and symptoms of disease and were categorized as improving to a lower disease severity level (14 of 36 [39%] patients vs. 4 of 22 [18%] patients, respectively). This difference, however, was not statistically significant ($P = 0.098$). When combined with those who did not have a change in the disease severity levels at month 12, significantly more patients treated with cyclosporine 0.05% had either improvements or no change in disease severity than did those treated with artificial tears (34 of 36 [94%] patients vs. 15 of 22 [68%] patients, respectively; $P = 0.007$).

Schirmer test scores

The mean baseline Schirmer test score was 7.7 ± 0.6 mm in patients randomized to artificial tears and 7.9 ± 1.2 mm

TABLE 2. PATIENTS' DISPOSITION AND DISEASE CHARACTERISTICS

	Artificial Tear	*Cyclosporine 0.05%*
Patients (*n*)		
Enrolled in study	33	41
Discontinued study	11[a]	5[b]
Completed study	22	36
Mean age[c] ± SD, years	48.2 ± 6.3	47.5 ± 5.9[d]
Range	39–59	30–57
Gender[c], *n* (%)		
Female	16 (73)	25 (69)[e]
Dry eye severity at baseline,[c] *n* (%)		
Level 2	15 (68)	24 (67)
Level 3	7 (32)	12 (33)

[a]Nine patients discontinued the study because of discomfort upon instillation. Two patients were lost to follow-up or moved. $P = 0.028$ compared to patients who received cyclosporine 0.05%.

[b]Two patients discontinued the study because of discomfort upon instillation. Three patients were lost to follow-up or moved.

[c]For patients who completed 12-month study.

[d]$P = 0.667$ compared to the mean age of patients who received artificial tears.

[e]$P = 0.800$ compared to the artificial tear group.

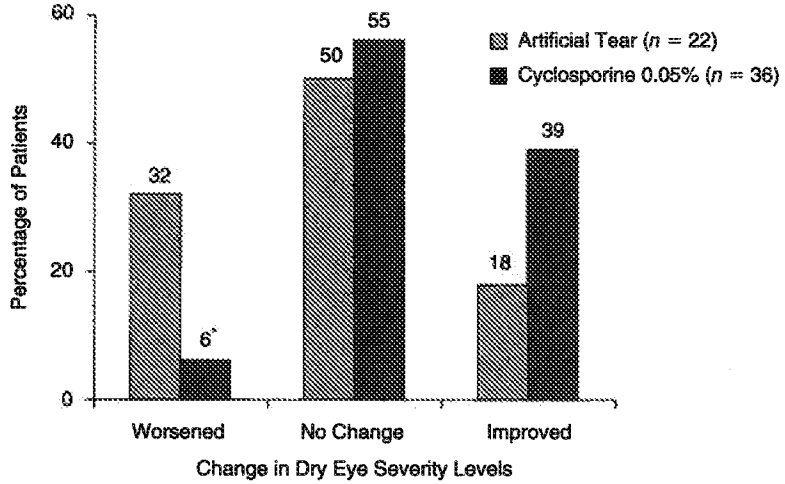

FIG. 1. Changes in dry eye severity at month 12 compared with baseline. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Disease severity was assessed according to the International Task Force (ITF) consensus guidelines at baseline and month 12. The changes in disease severity levels were categorized as worsened, no change, or improved when a patient had a, respectively, higher, same, or lower disease severity level at month 12 compared with baseline. *$P < 0.007$ compared with the treatment with artificial tears.

in patients randomized to cyclosporine 0.05% ($P = 0.625$). Patients treated with artificial tears did not have a significant change in their Schirmer test scores throughout the study, whereas those treated with cyclosporine 0.05% had increasingly higher mean Schirmer test scores at each follow-up visit. The mean Schirmer test scores of patients treated with cyclosporine 0.05% were significantly greater than those of patients treated with artificial tears at month 8 (9.1 ± 1.0 mm vs. 7.5 ± 1.1 mm; $P < 0.001$) and month 12 (9.8 ± 1.0 mm vs. 7.6 ± 1.1; $P < 0.001$; Fig. 2).

TBUT

The mean baseline TBUT was 5.0 ± 0.8 s in patients randomized to artificial tears and 4.9 ± 0.8 s in patients randomized to cyclosporine 0.05% ($P = 0.550$). The mean TBUT of patients treated with artificial tears slightly decreased throughout the study, whereas patients treated with cyclosporine 0.05% had increasingly longer mean TBUT at each follow-up visit (Fig. 3). The mean TBUT of patients treated with cyclosporine 0.05% was significantly longer than those of patients treated with artificial tears at months 8 (6.2 ± 1.4 s vs. 4.6 ± 0.6 s; $P = 0.001$) and 12 (6.5 ± 1.1 s vs. 4.6 ± 0.7 s; $P < 0.001$).

Ocular surface staining scores

At baseline, patients randomized to cyclosporine 0.05% or artificial tears had similar mean Oxford staining scores

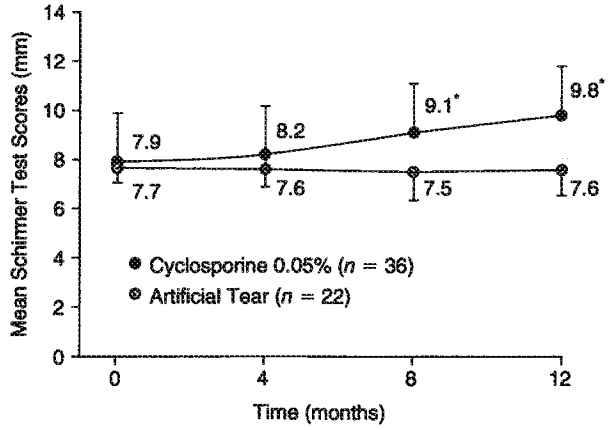

FIG. 2. Schirmer test scores. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Schirmer I test was performed with anesthesia at indicated study visits. *$P < 0.001$ compared with patients treated with artificial tears.

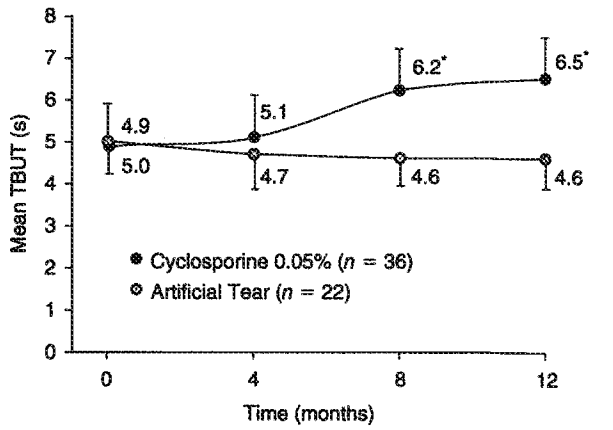

FIG. 3. TBUT. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Tear breakup time Tear breakup time (TBUT). was measured with fluorescein dye at indicated study visits. *$P \leq 0.001$ compared with patients treated with artificial tears.

TABLE 3. MEAN OCULAR SURFACE STAINING SCORES

	Artificial tear (n = 22)	*Cyclosporine 0.05% (n = 36)*	*P*
Baseline	7.86 ± 1.13 (NA)	8.44 ± 0.94 (NA)	0.056 (NA)
Month 4	7.73 ± 0.99 (–0.12 ± 0.64)	8.31 ± 0.95 (–0.13 ± 0.35)	0.036 (0.787)
Month 8	7.53 ± 1.01 (–0.25 ± 0.94)	7.78 ± 0.93 (–0.64 ± 0.63)	0.576 (0.087)
Month 12	7.54 ± 0.91 (–0.32 ± 0.94)	7.28 ± 1.28 (–1.19 ± 1.36)	0.223 (0.011)

Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Ocular surface damage was assessed at indicated times by the Oxford method. The mean changes from baseline and corresponding *P* values are indicated in brackets.[a] The change from baseline was calculated by subtracting the baseline score from the month 4, 8, or 12 scores.

NA = not applicable.

[a]The changes form baseline were paired comparisons. If a data point was missing, the baseline was also excluded from that calculation.

(8.4 ± 0.9 vs. 7.9 ± 1.1; $P = 0.056$; Table 3). At month 4, patients treated with cyclosporine 0.05% had significantly higher mean staining scores than those treated with artificial tears (8.3 ± 1.0 vs. 7.7 ± 1.0; $P < 0.036$). There was no between-group difference in ocular staining at months 8 and 12 (Table 3). Nonetheless, the mean improvement from baseline in the ocular staining scores of patients treated with cyclosporine 0.05% was significantly greater than of those treated with artificial tears at month 12 (1.2 ± 1.4 vs. 0.3 ± 0.9, respectively; $P = 0.011$; Table 3). These findings indicate that cyclosporine 0.05% improved ocular surface staining significantly more than did artificial tears at month 12 compared with baseline.

OSDI Scores

Patients randomized to artificial tears or cyclosporine 0.05% had similar OSDI scores at baseline (19.1 ± 1.9 and 18.9 ± 2.9, respectively; $P = 0.571$). The mean OSDI scores of patients treated with artificial tears remained unchanged throughout the study (Fig. 4). Patients treated with cyclosporine 0.05%, however, had increasingly lower OSDI scores at each study visit, with the scores at months 8 and 12 being significantly lower than those of patients treated with artificial tears (17.4 ± 3.4 vs. 19.6 ± 1.6 at month 8; $P = 0.011$ and 14.9 ± 4.2 vs. 19.7 ± 2.0 at month 12; $P < 0.001$).

Goblet cell density

At baseline, patients randomized to artificial tears or cyclosporine 0.05% had similar mean goblet cell density in bulbar conjunctiva (95.8 ± 12.5 cells and 93.6 ± 9.4 cells, respectively; $P = 0.446$; Fig. 5). By month 12, goblet cell density was significantly higher in patients treated with cyclosporine 0.05% than those treated with artificial tears (116.8 ± 14.8 cells vs. 92.7 ± 11.0 cells; $P < 0.001$).

Safety

No adverse events attributable to the study medications were reported other than discomfort upon instillation during the study.

Discussion

Dry eye is a multifactorial disorder of the tears and the ocular surface that results in tear film instability and symptoms of discomfort and visual disturbance.[22] Traditionally, treatment of dry eye has been palliative and largely based on over-the-counter artificial eyedrops and lubricating ointments.[23] The vast majority of patients seek new therapies after using several over-the-counter products over years.[23] However, it is not known if dry eye severity progresses through the course of disease during the years. Recently developed ITF guidelines provide a clinical standard for

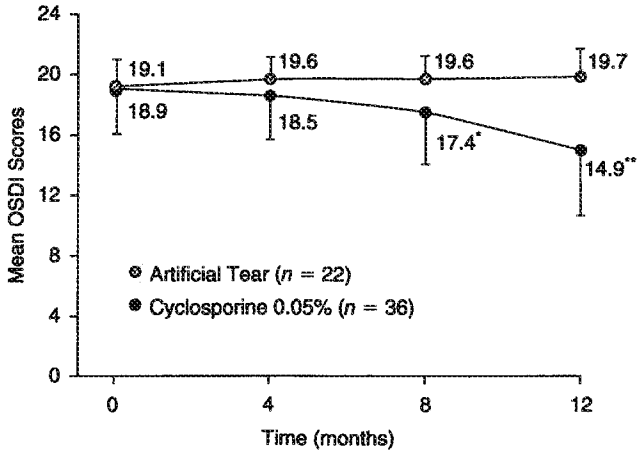

FIG. 4. Ocular Surface Disease Index (OSDI) scores. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Dry eye signs and symptoms were assessed by the self-reported OSDI questionnaire at indicated study visits. *$P < 0.011$ and **$P < 0.001$ compared with patients treated with artificial tears at months 8 and 12, respectively.

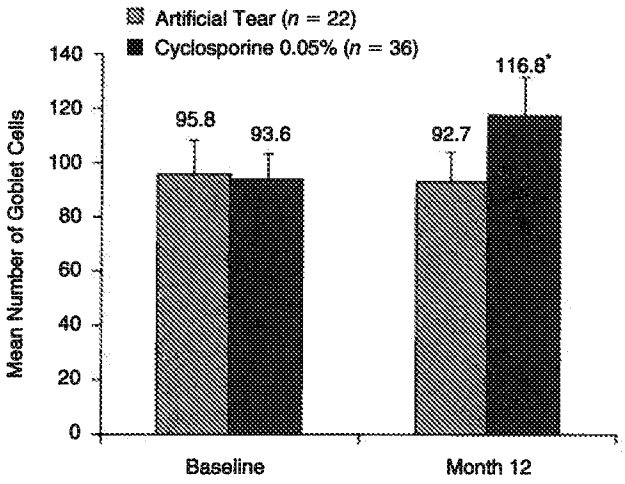

FIG. 5. Conjunctival goblet cell density at baseline and month 12. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Conjunctival goblet cells were collected by impression cytology and counted following staining with modified periodic acid–Schiff Papanicolaou at baseline and month 12. *$P < 0.001$ compared with artificial tears at month 12.

categorization of dry eye patients based on the disease severity and thereby allow longitudinal studies to evaluate the progression of dry eye disease. This study not only sought to assess the progression of dry eye disease in patients treated with artificial tears, but also evaluated the impact of cyclosporine 0.05% therapy in modulating the course of dry eye disease.

Treatment of dry eye patients with cyclosporine 0.05% improved Schirmer test scores, TBUT, conjunctival goblet cell density, ocular surface staining scores, and OSDI scores throughout the study. Treatment with artificial tears was not effective in improving the signs and symptoms of dry eye disease. Similar to these findings, several other studies demonstrated that cyclosporine 0.05% significantly increased tear production, decreased the intensity of ocular staining, and decreased the severity of symptoms in patients with moderate to severe dry eye.[24,25] A recent prospective study indicated that cyclosporine 0.05% therapy significantly improved signs and symptoms in patients at all stages of dry eye disease: mild, moderate, and severe.[26] Other studies have shown that treatment with cyclosporine 0.05% also increased conjunctival goblet cell density in patients with dry eye disease.[21,27]

Physicians participating in a study to develop treatment regimens based on the ITF consensus guidelines for newly diagnosed dry eye patients chose to treat over 40% of patients at severity level 1 with the severity level 2 treatments (ie, unpreserved tears and topical cyclosporine 0.05%).[13] Hence, the use of ITF guidelines resulted in greater focus on treatment of the disease at early stages. This shift in the patterns of anti-inflammatory therapy use stems from the notion that early interruption of inflammatory cycles may be instrumental in preventing disease progression.[13] The impact of dry eye in limiting daily activities and causing discomfort is known to become clinically more significant as the disease progresses from mild to moderate in severity.[2]

In addition to alleviating dry eye signs and symptoms, topical cyclosporine 0.05% therapy appears to be capable of slowing the rate of disease progression. Reassessment of patients at the end of the study period (month 12) indicated that a greater number of cyclosporine patients compared with the artificial tear patients (94% vs. 68%) had improvements or no change in their disease severity status, and far fewer (6% vs. 32%) experienced disease progression. These findings suggest the progressive nature of dry eye disease and indicate that dry eye patients may benefit from cyclosporine 0.05% therapy by achieving disease stabilization or a slower rate of progression. A recent retrospective study provided evidence that cyclosporine 0.05% therapy may change the course of dry eye disease. In that study, 8 chronic dry eye patients diagnosed at severity level 2 or 3 were free of signs and symptoms of dry eye disease for a minimum of 1 year after completing a 6- to 72-month course of cyclosporine 0.05% therapy.[28]

In some patients, dry eye is a difficult-to-treat disease that requires long-term anti-inflammatory therapy. The safety profile of a topical anti-inflammatory agent and its suitability for long-term use is, therefore, a key factor in successful management of dry eye disease. Topical corticosteroids have been effective in alleviating the signs and symptoms of dry eye following short-term use (2–4 weeks).[29,30] Prolonged administration of topical corticosteroids is complicated by the associated adverse events including elevation of intraocular pressure, defects in visual acuity and fields of vision, cataract formation, and increased risk of ocular infections.[29,31] Topical cyclosporine 0.05%, however, appears to be safe for a long-term use. Several clinical studies demonstrated that cyclosporine 0.05% was well tolerated for up to 3 years with most adverse events being transient in nature and mild to moderate in severity.[24,25,32]

The present study had a number of limitations. The sample size was small, as this was a pilot study to assess the feasibility of the study design. It should also be noted that the differences between the treatment groups reported in this study can be applied only to the use of Refresh Endura® as the artificial tears. Other artificial tears may have variable efficacies in alleviating the signs and symptoms of dry eye.

Strategies to treat dry eye disease are evolving as our understanding of dry eye as a tear volume insufficiency condition is changing to a disease of abnormal tear film composition with proinflammatory characteristics.[10,33,34] The findings of the current study are the first evidence indicating that dry eye can be progressive in patients treated with artificial tears alone, whereas topical anti-inflammatory therapy with cyclosporine 0.05% may slow or prevent the disease progression in patients with dry eye at severity level 2 or 3. Large-scale, controlled studies are warranted to confirm these findings.

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Author Disclosure Statements

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EXHIBIT F

The Impact of Dry Eye Disease on Visual Performance While Driving

NATHALIE DESCHAMPS, XAVIER RICAUD, GHISLAINE RABUT, ANTOINE LABBÉ, CHRISTOPHE BAUDOUIN, AND ALEXANDRE DENOYER

• PURPOSE: **A specific simulator was used to assess the driving visual performance in patients with dry eye disease (DED) and to determine clinical predictors of visual impairments while driving.**

• DESIGN: **Prospective case-control study.**

• METHODS: **The study was conducted in the Center for Clinical Investigation of Quinze-Vingts National Ophthalmology Hospital, Paris, France. Twenty dry eye patients and 20 age- and sex-matched control subjects were included. Vision-related driving ability was assessed using a specific driving simulator displaying randomly located targets with a progressive increase in contrast to be identified. Other examinations included clinical examinations, serial measurements of corneal higher-order aberrations (HOAs), and vision-related quality-of-life questionnaire (Ocular Surface Disease Index [OSDI]). Data collected during driving test (ie, the number of targets seen, their position, and the response time) were compared between groups and analyzed according to clinical data, aberration dynamics, and quality-of-life index.**

• RESULTS: **The percentage of targets missed as well as average response time were significantly increased in DED patients as compared with controls ($P < .01$). More specifically, the visual function of DED patients was more impaired in specific situations, such as crossroad or roundabout approaches. In DED patients, the response time was found to positively correlate with the progression index for HOAs ($P < .01$) and with the OSDI "symptoms" subscale ($P < .05$).**

• CONCLUSIONS: **Degradation of ocular optical qualities related to DED is associated with visual impairments during driving. This study objectively has demonstrated the impact of tear film–related aberration changes on activities of daily living in DED. (Am J Ophthalmol 2013;156: 184–189. © 2013 by Elsevier Inc. All rights reserved.)**

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DRY EYE DISEASE (DED) IS RECOGNIZED AS a growing public health problem and one of the most frequent reasons for seeking eye care. The DED definition has evolved with recent epidemiologic studies as well as a better understanding of the pathophysiology of the disease. It is estimated to affect from 5% to over 30% of the population, depending on the diagnostic criteria.[1] This common health problem is likely to be overlooked because it tends not to be a common cause of visual morbidity as standardly measured. Nevertheless, there is increasing evidence that DED is a major cause of visual disturbance, which degrades the quality of everyday life and can impact health status.[2]

According to a recent overview arising from the 2007 International Dry Eye Workshop, DED causes damage to the ocular surface and symptoms of ocular discomfort associated with impaired visual quality.[3] Indeed, patients with DED often report vision-related difficulties in doing daily activities. In clinical practice, the main difficulty in managing DED stems from the variability of the symptoms, the lack of a single reliable diagnostic test, and weak correlations between clinical tests, optical and biological examinations, and patient-reported deterioration in quality of life.[4–6] The precorneal tear film plays an important role in ocular optical quality since it is the most anterior refractive surface of the eye.[7,8] In the majority of patients with DED, the visual acuity is still 20/20 as standardly measured, but instability of the tear film introduces wavefront higher-order aberration (HOA) changes that always contribute to a decrease in the quality of vision.[9,10] Our team recently demonstrated that a specific analysis of the time course of HOAs provides objective and quantitative data that are correlated with both clinical signs and patient-reported outcomes, raising the possibility of using this instrument as a new surrogate marker for the disease.[11]

Beyond conventional clinical examination and visual acuity measurement, a specific evaluation of the visual function in daily living tasks is now required to better define the impact of the disease on this population's health status but also to better assess eligibility or changes over time in clinical trials. Although DED patients commonly complain of difficulties in doing vision-related daily activities, as previously reported using quality-of-life questionnaires,[12] no study has been conducted to determine whether or not DED could be responsible for an objective decrease in visual performance while driving. The present study addresses the impact of DED on a crucial daily

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activity of modern living. A driving simulator dedicated to visual function evaluation was used in patients with DED and in age- and sex-matched healthy controls in order to better specify the relationship between driving difficulties, objective ocular signs and optical degradation, and patient-reported vision-related quality of life.

METHODS

• PATIENTS: The study was conducted in the Clinical Center for Investigation of Ocular Surface Pathology (Quinze-Vingts National Ophthalmology Hospital, National Institute for Health and Medical Research 503, Paris, France) in accordance with the Declaration of Helsinki, Scotland amendment, 2000. Previous approval was obtained from the National Ethical Research Committee (Comité de Protection des Personnes Ile de France V, agreement number 10793). All patients gave informed consent to participate in this clinical research study. Twenty white patients with DED and 20 white age- and sex-matched control subjects were prospectively and consecutively included. DED was diagnosed by the association of ocular symptoms and tear film abnormalities (Schirmer I test <5 mm/5 min and/or tear break-up test <10 s), with or without ocular surface damage (corneal and conjunctival staining), according to the DEWS criteria from the modified Delphi Panel Report.[4,13] Only the subjects with a best-corrected visual acuity of at least 0 logMAR were included, since this study focused on a decrease in visual function related to tear film degradation and ocular symptoms but not to extensive corneal damage. At inclusion time, all patients were treated with tear substitutes only, without any anti-inflammatory or cyclosporin medication, and without changes within the last 3 months. Healthy age- and sex-matched subjects with no ocular pathology, with no treatment, and without any symptoms or signs of DED (Schirmer I test >10 mm/5 min and Oxford score = 0) were included as controls. All participants were in good general health and were licensed drivers with at least weekly driving practice. Exclusion criteria were any ocular pathology but DED, eyelid malposition or dynamic disorders, previous ocular/eyelid surgery, contact lens wear, systemic disorder, pregnancy, and treatment changes within the last 3 months.

• CLINICAL EXAMINATION AND QUESTIONNAIRE: Slit-lamp evaluations were conducted in a defined sequence[14] and included tear break-up time measurement (s, mean of 3 consecutive tests), ocular surface fluorescein staining (grade 0-5, according to the Oxford score), lissamine green staining (grade 0-9, according to the van Bijsterveld score), and Schirmer I test (mm/5 min, without anesthesia). Before clinical examination, a trained interviewer (G.R.) administered the French version of the Ocular Surface Disease Index (OSDI) questionnaire, which was developed to quantify the specific impact of DED on vision-targeted health-related quality of life.[15] This disease-specific questionnaire includes 3 subscales: ocular symptoms (OSDI-symptoms), vision-related activities of daily living (OSDI-function), and environmental triggers. Each subscale (0-100) was computed, as well as an overall averaged score (0-100).

• DYNAMIC ABERROMETRY: Serial measurements of corneal and ocular wavefront aberrations were simultaneously performed every second for 10 s after blinking using the dynamic aberrometer KR-1 (Topcon, Clichy, France). The entire procedure has been previously described.[11] Briefly, HOAs were recorded in mesopic conditions without any pharmacologic mydriasis, analyzed by expanding the set of Zernike polynomials up to the sixth order, and expressed for the central 4-mm diameter. The progression index of total (third- to sixth-order) HOAs was defined as the slope of the linear regression line of HOAs throughout the recording period, as previously defined.[11]

• DRIVING TEST: We used a driving simulator purchased from Develter Innovation (Ile de France, France). This simulator has an automatic shift. Driving tests were performed with the best spectacle correction in scotopic conditions on a standardized 5-km circuit. Each test had a series of 7 lighted targets, increasing in intensity for 15 s and then disappearing. Lighted targets randomly appeared during the test at various positions and various driving conditions: straight forward, straight backward, at a crossroad entrance, and on the right-hand or left-hand side of a crossroad. For each target seen, the patient had to press a remote button on the wheel. Data included the number of targets seen/missed, their respective location, and the average response time. The results were determined as the mean of 3 consecutive tests.

• STATISTICAL ANALYSIS: All data are given as the mean ± SD. For ocular examinations—clinical evaluation, tear osmolarity measurement, and wavefront aberrometry—1 eye per patient was selected using a random number table in order not to bias the statistical relevance of the results. Data were controlled for normality, homogeneity of variances, and sphericity in order to perform the adequate tests. The 2 groups were compared using parametric *t* tests. In the DED group, scatterplots and Spearman correlation coefficients were used to assess the association between pairs of variables. The probability level of significance was adjusted according to the post hoc Bonferroni procedure in order to maintain an overall type I error equal to 0.05.

RESULTS

THE PROFILE, CLINICAL FEATURES, AND OSDI SCORES OF each group are detailed in the Table. Six patients presented

TABLE. Subject Profiles and Ocular Surface Disease Index Scores Between Dry Eye Patients and Age- and Sex-matched Controls

	Dry Eye Patients (n = 20), Mean ± SD (min/max [95% CI])	Controls (n = 20), Mean ± SD (min, max [95% CI])
Age (y)	53.4 ± 16.2 (22/84 [46.3-60.5])	53.1 ± 16.4 (22/84 [45.9-60.3])
Sex ratio (m/f)	0.25	0.25
Clinical data		
Tear break-up time (s)	5.9 ± 2.2 (2/10 [5.0-6.9])	11.4 ± 3.7 (4/15 [9.9-13.1])
Schirmer (mm)	9.5 ± 5.4 (1/20 [7.2-11.9])	19.6 ± 0.6 (15/20 [19.4-19.9]
Oxford (0-5)	1.1-0.8 (0-4 [0.7-1.4])	0
Van Bijsterveld (0-9)	2.7 ± 1.6 (0-6 [1.9-3.3])	0.1 ± 0.1 (0/1 [0-0.1])
Ocular Surface Disease Index		
Overall score	48.1 ± 18.4 (10.4/89.6 [40.6-56.6])	2.2 ± 2.9 (0/10.4 [0.9-3.3])
OSDI symptoms	43.3 ± 15.6 (15/80 [36.4-50.1])	2.1 ± 3.1 (0/15 [0.8-3.5])
OSDI functions	41.3 ± 27.8 (0/93.8 [29.1-53.4])	1.8 ± 2.9 (0/12.5 [0.5-3.1])
OSDI triggers	58.3 ± 29.2 (8.3/100 [45.6-71.1])	2.4 ± 3.9 (0/16.7 [0.7-4.1])

OSDI = Ocular Surface Disease Index.

mild-severity DED and 14 patients presented moderate-severity DED, according to the Delphi approach.[5] Significant differences in all the clinical characteristics and OSDI scores were found between DED patients and controls (paired t test, $P < .01$ for each).

• COMPARATIVE ANALYSIS OF ABERRATION DYNAMICS BETWEEN GROUPS: Significant variation with time in corneal total HOAs (repeated-measures ANOVA, $P < .01$), third-order coma ($P < .01$), and third-order trefoil ($P < .01$) was found in DED patients, whereas no significant change occurred in the control group throughout the recording period. As detailed in Figure 1, the progression index of corneal total HOAs and of corneal third-order trefoil was significantly higher in DED patients than in healthy controls ($P < .01$ and $P < .05$, respectively).

• DRIVING VISUAL PERFORMANCE: The average response time to identify targets was significantly higher in DED patients than in controls ($P < .01$) (Figure 2, Left). Moreover, a significant difference in the average number of targets seen was found between groups ($P < .01$), further depending on target location (Figure 2, Right): interestingly, targets appearing at a crossroad entrance and at the right-hand side of a crossroad were more often missed by DED patients than by healthy subjects ($P < .01$ and $P < .05$, respectively). On the contrary, targets appearing straight on (forward or backward) were equally detected in the 2 groups.

In DED patients, a positive correlation was found between the response time to identify targets and the progression index for corneal HOAs ($R^2 = 0.40$, $P < .01$) as well as between response time and the OSDI "symptoms" subscore ($R^2 = 0.25$, $P < .05$) (Figure 3). No significant correlation was found between the driving simulation data and the other computed data (Supplemental Table, available at AJO.com). Following a stepwise regression procedure, the response time was found to significantly depend on the progression index for corneal HOAs only (R^2 increment = 0.40, $P < .01$).

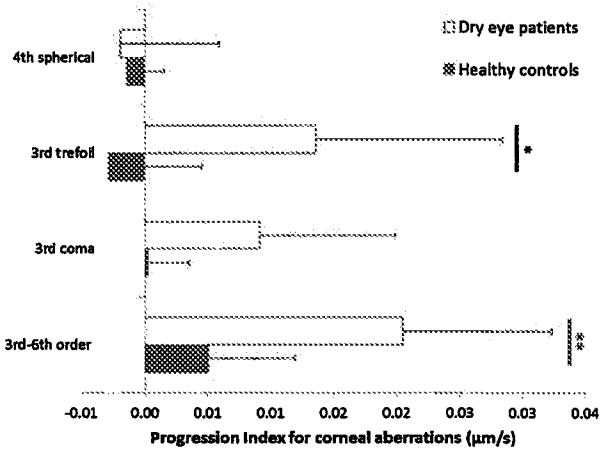

FIGURE 1. Comparative analysis of corneal aberration dynamics between dry eye patients and age- and sex-matched controls. Significant difference in the progression index for third- to sixth-order higher-order aberrations and for third-order trefoil between dry eye patients and controls (paired t test, *$P < .05$, **$P < .01$).

DISCUSSION

DED IS A CHRONIC OCULAR SURFACE DISEASE THAT affects millions of people worldwide.[1] The majority of patients with DED experience chronic ocular discomfort associated with impaired daily visual function and subsequent vision-related quality-of-life disturbance, further

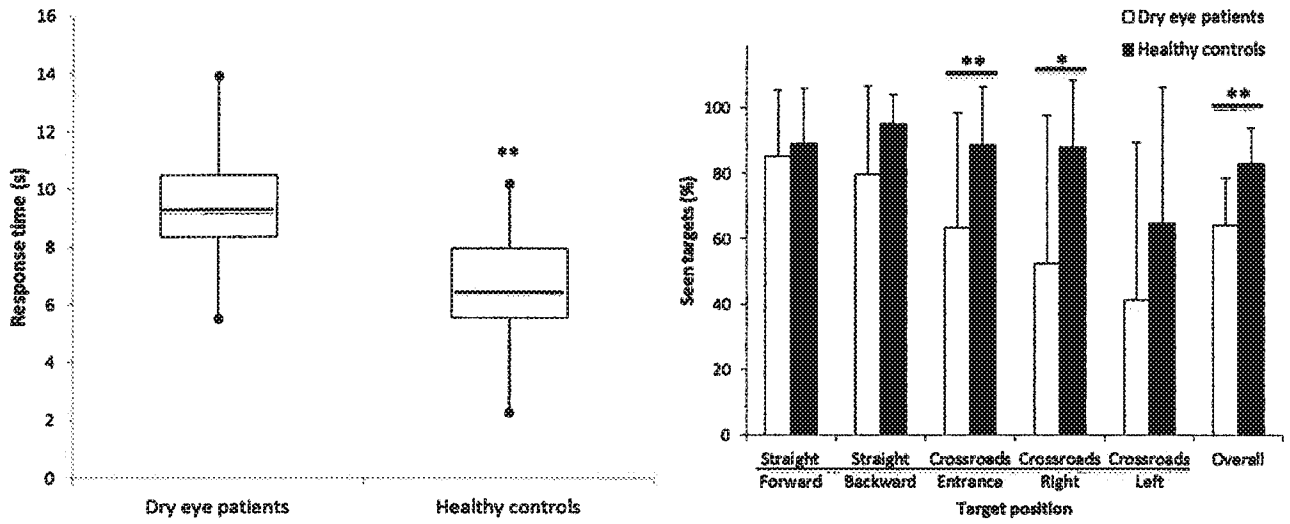

FIGURE 2. Comparative analysis of visual performance while driving between dry eye patients and age- and sex-matched controls. (Left) Average response time to identify targets in dry eye patients and in controls. Data are presented as median, 95% confidence interval, and range. (Right) Percentage of targets seen depending on target location (paired *t* test, $*P < .05$, $**P < .01$).

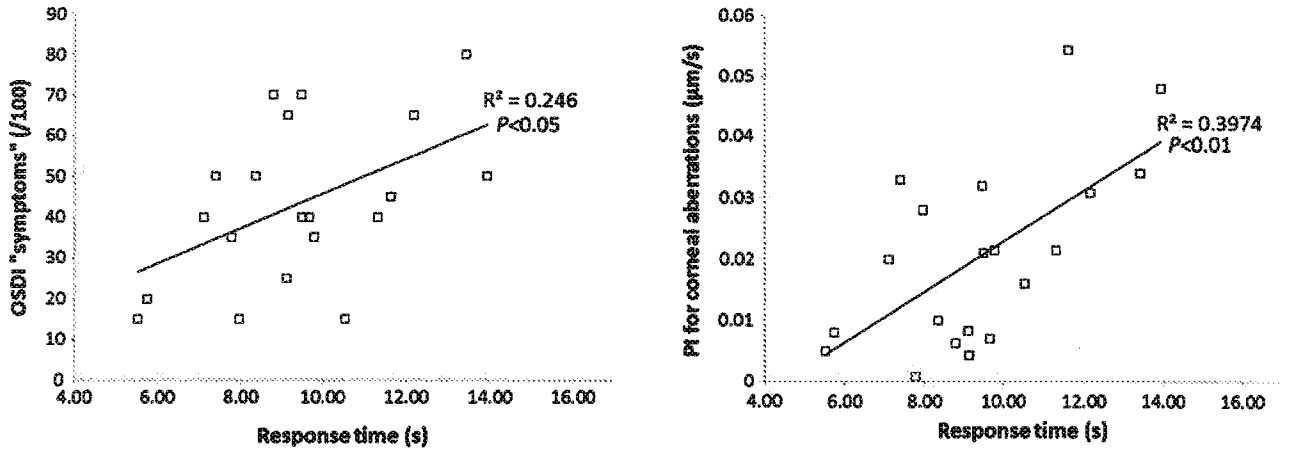

FIGURE 3. Linear relations between visual performance while driving and the other data in dry eye patients. Visual performance while driving, as assessed by the response time to identify targets during a driving simulation, was analyzed in correlation with the other data. (Left) Positive correlation between the response time and Ocular Surface Disease Index (OSDI) "symptoms" subscore (Spearman correlation test, $P < .05$). (Right) Positive correlation between the response time and progression index (PI) for corneal higher-order aberrations ($P < .01$).

impacting health status.[2] The present study objectively reports that the visual function is impaired during specific driving situations in DED patients as compared with healthy controls, further demonstrating that driving visual performance is correlated with ocular optical aberrations and patient-felt quality of life in this disease.

Tear film instability is reported to increase the progression with time of corneal HOAs after a blink.[16–18] The present study originally found a relation between tear film–related ocular optical degradation and driving difficulties. An increased blink rate is thought to compensate for corneal dryness, which stimulates tear secretion and creates a new tear film layer.[19] Goto and associates[19] found a deterioration of visual function during the fixation without blinking in 22 DED patients compared with 8 controls. The deterioration of vision after blinking supports the hypothesis that the tear film of patients with DED is unstable, especially when blinking is delayed. Precisely, we reported herein that DED patients missed more frequently targets at crossroad entrances than targets appearing straight on. We could hypothesize that this result is linked with a decrease in blink rate and subsequent increase in corneal HOAs when

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a specific driving situation requires more attention. Indeed, the elapsed time between blinks is known to increase in specific conditions, such as high driving speed.[19] In the present study, it could also have been interesting to record blink rate during the simulation to more precisely examine this point. Hence, other aspects of vision than standard visual acuity may be taken into account to better reflect the daily visual function, as clearly detailed by Owsley and McGwin.[20]

The association between loss of contrast sensitivity and driving disability has been previously studied on the one hand, and a decrease in contrast sensitivity has been reported in DED patients on the other hand. However, nothing was known about a direct link between DED-related contrast sensitivity impairments and driving difficulties. Although conventional contrast sensitivity testing was not performed in the present study, we reported a pronounced increase in response time in the DED group, which corresponds to the need for higher signal intensity to be perceived since the target contrast was increasing with time during a 15-second period. Rubin and associates studied the relationships between various indexes of visual function and driving ability in a population of 222 healthy volunteers.[21] The authors reported contrast sensitivity as the strongest correlating factor for subject-felt driving difficulty. Indeed, standard visual acuity, the most commonly used measure of visual function, does not correlate with some types of functional disability, such as driving.[21,22] Owsley and associates also reported that people with low contrast sensitivity have 8 times more road accidents than other people.[23,24] In dry eye, Rolando and associates compared 30 DED patients (18 patients with corneal damage and 12 without) with 15 healthy subjects.[22] They showed a significant decrease in contrast sensitivity in both DED groups as compared with controls. Interestingly, the authors confirmed that the quality of vision was reduced in DED whatever the visual acuity as standardly measured. In the present study, it could also have been interesting to perform conventional contrast testing, but our primary goal was to assess the visual performance in more realistic conditions. Our study confirms that visual impairments in patients with DED are not accurately evaluated by routine examination, further indicating the need for new visual criteria to better reflect visual function in daily living.

The subjective relationship between DED and driving difficulties has been previously described through the use of vision-related quality-of-life questionnaires.[12,25] Complementarily, our study is the first, to our knowledge, to objectively assess visual function in DED patients while driving, further establishing a direct link between DED, ocular optical degradation, and driving difficulties. Miljanovic and associates assessed vision-related quality of life with a questionnaire in a series of 190 DED patients vs 399 controls. They reported a decrease in driving ability in DED patients as compared with controls.[25] Herein several quantitative standardized measures of visual quality were correlated with patients' subjective perceptions, showing a significant correlation between the patient-reported OSDI symptoms score and visual difficulties during daytime driving as objectively assessed by a driving simulation. Difficulty in viewing lighted targets may be related to a disability in seeing or identifying external signals such as lights or traffic signs, but also pedestrians or other vehicles, when driving. Although subjects may have more difficulty while driving, it does not necessarily mean that they cannot drive safely. Future studies should evaluate the correlation with accidents rates. Such an approach could aid in developing efficient counseling for patients with DED and also in improving the driver's environment by providing, for example, high-contrast signs. The delayed reaction time found in DED patients could be linked with subject-felt discomfort when driving regularly, which could explain a feeling of insecurity and some loss of confidence in patients with ocular dryness. Since this feeling is reported to be enhanced when driving at night, it could be interesting to perform such a simulation in mesopic/scotopic conditions. Otherwise, a future study using artificial tears in driving conditions may aid in determining whether such a driving simulator could be useful in the evaluation of treatments.[26]

A current challenge for a physician in managing DED stems from the difficulty in making allowances for both objective clinical findings and patients' complaints in order to assist the patient as best as possible and optimize the therapeutic strategy. Today's lifestyle—which includes intensive daily visual activities, such as reading, driving, and using a computer/smart phone—requires excellent visual performance to achieve well-being. Our results better elucidate one of the reasons in which DED is responsible for a decrease in patient-perceived quality of life by establishing a direct link between DED, ocular optical degradations, and impairment in visual performance while driving. Hence we demonstrate that, beyond the conventional visual acuity measurement, specific ocular optical degradations related to DED may impact on daily living tasks, such as driving. We believe that such objective measures of visual performance could be relevant to better evaluate the severity of the disease and the impact of DED on this population's health status worldwide.

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EXHIBIT G

Utility Assessment among Patients with Dry Eye Disease

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Purpose: To determine utilities (patient preferences) for dry eye disease.

Design: Survey study.

Participants: Fifty-six patients with mild, moderate, or severe dry eye treated by ophthalmologists in the Eye Care Services department of Henry Ford Health Care System.

Testing: Patients completed interactive software utility assessment questionnaires by the time trade-off (TTO) method. Utility scores were scaled such that a score of 1.0 = perfect health and 0 = death. Dry eye severity was independently classified using clinical parameters and physician/patient assessments. Global health status, visual functioning, and ocular symptoms were assessed by the Short Form-36 Health Survey, 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), and Ocular Surface Disease Index survey instruments.

Main Outcome Measures: Utility scores for a range of dry eye severity states. These utilities were compared with utilities reported for other disease states. Correlations with the general and vision-related health status measures were conducted.

Results: Fifty-six patients completed the utility assessments with acceptable reliability. Mean utilities for moderate (0.78) and severe dry eye (0.72) by TTO were similar to historical reports for moderate (0.75) and more severe (class III/IV) angina (0.71), respectively. Utility scores correlated with the NEI VFQ-25 composite score ($\rho = 0.32$; $P = 0.037$) and with components of other health measures.

Conclusions: Utilities for the more severe forms of dry eye are in the range of conditions like class III/IV angina (0.71) that are widely recognized as lowering health utilities. Our results underscore how significantly dry eye impacts patients compared with other medical conditions. *Ophthalmology 2003;110:1412–1419 © 2003 by the American Academy of Ophthalmology.*

Dry eye disease is one of the most frequently encountered ocular morbidities, with as many as 4.3 million Americans older than age 65 with symptoms either often or all the time.[1] The dry eye syndrome is composed of a number of diverse medical and ocular diseases that involve decreased tear production and/or increased tear evaporation.[2] Because of the wide-ranging etiologies of dry eye and the great variability of clinical signs of the condition, it has been difficult to develop a consistent classification system for dry eye or reliable and valid measures of disease severity. This has complicated efforts to determine the incidence and prevalence of dry eye, to monitor disease progression and response to treatment, and to adequately quantify the impact that dry eye has on patients' quality of life. To this end, we have used several validated instruments to evaluate dry eye,[3] including the health-related Short Form-36 Health Survey (SF-36),[4] the vision-related quality-of-life measure NEI VFQ-25,[5] the Ocular Surface Disease Index (OSDI), and the Patient Perception of Ocular Symptoms.[3] Although nearly all of these measures yield a multidimensional profile of health status, none yields a single measure of how patients value various health states or outcomes.

Utility assessment is a formal method for quantifying patient preferences for health outcomes. For assessment at the societal or policy level, scale utility scores are typically anchored at perfect health (utility = 1) and death (utility = 0) and are measured on an interval scale.[6] Investigators might also assess clinical scale utility scores with less extreme anchors, such as the presence or absence of a condition of interest, for example, perfect vision (utility = 1) and blindness (utility = 0). The closer the utility value is to 1.0, the better the quality of life associated with that health state. Once utilities are scaled by use of comparable anchors, the impact of very different health states on quality of life can easily be compared.

Utilities can be measured in a number of ways. The time trade-off (TTO)[7] and standard gamble methods are the most

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widely used. Numerous researchers have concluded that patients most readily understand TTO.[8–11] Hence, the TTO method was used in this study. In TTO, the subject is offered two choices: (1) living t years, the life expectancy for a person in the current disease state followed by death, or (2) being in perfect health for fewer years ($x < t$) followed by death. The time in complete health, x, is varied until the subject is indifferent between the two choices. The utility weight is then x/t. A benefit of TTO compared with other utility tests is that it is more intuitive to patients while still capturing their risk preference. A limitation of TTO is that results might be biased upward, because subjects are asked to give up years at the end of life, which might be valued less.[11,12]

The purpose of this study was to measure utilities by TTO for the full severity range of dry eye states in a group of patients with dry eye and to determine how utilities correlate with disease severity and other health and vision quality-of-life measures. These utilities then could be used to compare patient preferences for dry eye disease outcomes with different symptomatic medical conditions, such as angina or blindness. They also could be used as weights in the calculation of quality-adjusted life years.[6] These quality-adjusted life years could be used as "denominators" in cost-utility analyses that allow health care policy makers to rigorously compare costs and health benefits across a wide range of medical interventions.

Material and Methods

Study Overview

Eligible participants completed several questionnaires between August 2000 and March 2001 to assess their sociodemographic status, general health status, visual functioning, and ocular symptoms. Next, they completed TTO utility assessments and underwent a detailed ophthalmic examination. Questionnaires and utility assessments were completed before the examination to ensure that the clinical encounter would not influence patients' responses. A convenience sample of patients returned 2 weeks later to complete the utility assessments a second time to determine test–retest reliability.

This study was conducted in compliance with the Code of Federal Regulations for sponsors and investigator obligations. Institutional review board/ethics committee approval was obtained. Written informed consent was obtained from all patients before enrollment.

Patient Selection

Patients were recruited if they were at least 18 years of age, had been diagnosed with dry eye (International Classification of Diseases, ninth revision = 375.15) at the Henry Ford Health System in the last 6 months and had symptoms for at least 3 months. Those scoring ≥8 on the OSDI were confirmed as symptomatic. A minimum score of 8 was chosen to ensure that all patients had at least mild symptoms, because a prior study found normal subjects to have an OSDI composite score of 4.5 ± 6.6 (mean ± standard deviation [SD]).[3] Participants had a life expectancy ≥1 year, corrected visual acuity of 20/40 or better in each eye, were English speaking, and were able to complete surveys without significant assistance. Those older than age 65 were screened with the Folstein mini-mental status examination questionnaire[13] to confirm that they were cognitively intact to participate in the study.

Exclusion criteria included uncontrolled systemic disease or disability affecting daily activities (such as ocular allergy, infection, irritation, or inflammation unrelated to dry eye disease). Also excluded were patients who had undergone ocular surgery (including cataract surgery) within the previous 6 months, who had undergone temporary or permanent punctal occlusion within the past 3 months, and those known to be allergic to any component of any study agent (e.g., lissamine green, fluorescein, or anesthetic).

Patient enrollment was prospective and consecutive from August 2000 to March 2001.

Main Outcome Measures

Utility Assessments for Dry Eye Disease. Utility assessments were made by means of the computerized interview U-titer software program (Computer Assisted Patient Education, Houston, TX), which provides a standard framework for measuring utilities,[14] taking into account patient life expectancy while permitting investigators the flexibility to program disease-specific scenarios for patients. U-titer has been used to measure utilities for psoriasis,[15] angina,[16] osteoporosis,[17] and prostate cancer.[18]

For the TTO utility assessments, patients reacted to a total of 9 scenarios or health states, including asymptomatic dry eye (requiring routine artificial tear use to completely avoid symptoms), mild dry eye (requiring only occasional treatment to treat periodic dry eye symptoms), moderate dry eye (requiring somewhat more frequent treatment for more persistent symptoms,) severe dry eye (requiring very frequent treatment for very severe symptoms), severe dry eye requiring tarsorrhaphy, monocular painful blindness, and binocular painful blindness. See Figure 1 for an example scenario and Figure 2 for a sample utility assessment question. Painful blindness was specified, because many symptomatic patients with dry eye perceive their dry eye symptoms as painful. Patients also assessed the utility of their current dry eye status. Finally, patients reacted to a scenario about their own comorbidities in the absence of dry eye. It is believed that patients can project what it would be like if they did not have the health condition being studied but had all other comorbidities.[7,16,19–21] As described later, this projection permitted us to estimate the utility for each of the health states in the absence of comorbidities.

Scaling of Utility Scores. TTO dry eye utility scores, which were reported on a scale with anchors of "death" and "perfect painless vision," were converted to a scale ranging from "death" to "perfect health." The latter scale is the traditional policy scale that permits comparisons with the broadest range of health states. This rescaling was conducted using the patients' own comorbidity utility score. The comorbidity utility score represents a subject's health were he or she to have all their current comorbidities but no dry eye. It represents the upper limit of what a patient's utility score could be before dry eye symptoms are taken into account. To rescale, the patient's utility score was multiplied by the reported comorbidity utility score to achieve a final utility score, which incorporates dry eye and all comorbidity and is scaled from "death" to "perfect health."[19]

Dry Eye–specific Utility Loss. If one fails to take comorbidity into account, it is possible to overestimate the lost utility because of the condition of interest and hence to overestimate the potential benefit of treatment.[19] To compute the magnitude of utility loss caused by dry eye alone, the patient's final utility score (comorbidity-adjusted dry eye utility score, the preference for having dry eye disease in the presence of associated comorbidities, on the "death" to "perfect health" scale) is subtracted from the patient's comorbidity utility score (the preference for being free of dry eye,

Severe Dry Eye

Imagine that your eyes feel dry, gritty or sore most or all of the time. Your vision is frequently blurred and fluctuates quite a bit. You use eye drops in both eyes every 1-2 hrs, but that provides only temporary and partial relief of your symptoms. You will use a lubricant at bedtime in both eyes. You will also undergo a painless 10-minute procedure in the doctor's office to block off the tear drainage system. There are no complications from this procedure.

Now imagine there's a treatment that would cure all of your symptoms of dry eye, including any vision problems you might have from dry eyes. You would no longer require any eye drops or any other medications for your dry eyes, nor would you require any procedures or surgeries for your eyes. This treatment, however, is accompanied by a reduction in your life expectancy (you will live a shorter life). Now, think about how much life expectancy you would be willing to trade in order to cure your symptoms of dry eye.

Figure 1. Sample scenario presented to patients undergoing the time trade-off utility assessment.

but still having all other comorbidities, also on the "death" to "perfect health" scale).

Additional Measures

Disease Severity. The severity of dry eye disease was rated by physician assessment and also by a composite disease severity score. The composite disease severity score, described previously,[3] is substantially less dependent on physicians' subjective assessments and is easily computed. It combines traditional clinical measures of dry eye (Schirmer's type-1 and ocular surface staining) with a symptom-based measure (patient perception of ocular symptoms) to evaluate dry eye in adherence with the recommendations of the National Eye Institute Workshop on Clinical Trials in Dry Eyes.[2]

Health Status Measures. General health-related quality-of-life was measured with the SF-36. Vision-related quality of life and ocular symptoms were assessed with the OSDI, the Patient's Perception of Ocular Symptoms, and the NEI VFQ-25. All surveys were completed by self-administration.

The SF-36 is a reliable, valid, and responsive measure of global health status that measures health status in 8 dimensions, including physical functioning, role limitation because of physical disability, bodily pain, general health, vitality, social functioning, emotional limitation because of emotional disability, and mental health. These measures are summarized by a physical component summary score and mental component summary score.[4]

The OSDI, developed by Allergan, Inc., is a reliable, valid, 12-item questionnaire designed to measure ocular disability from ocular surface disease (Drug Information J 1997;31:1436). The

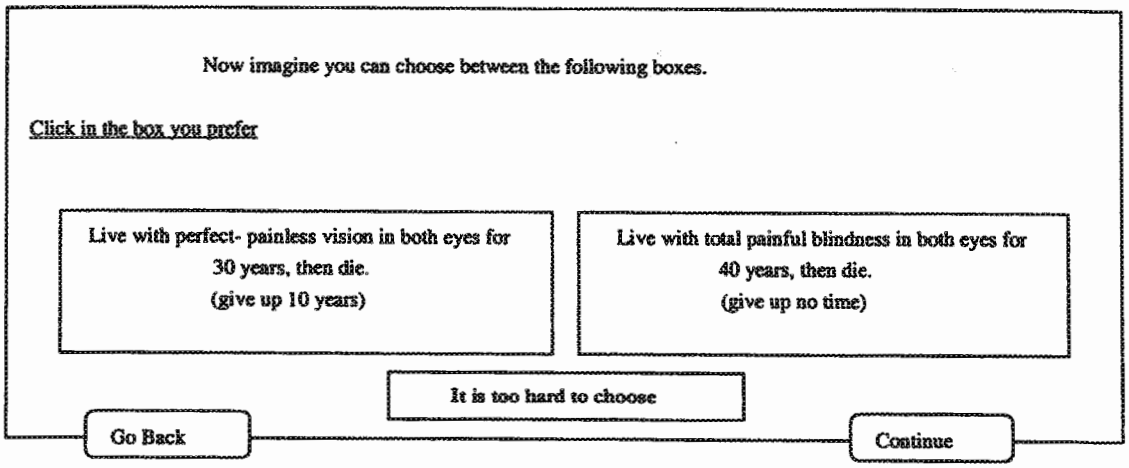

Figure 2. Sample question posed by U-titer in the time trade-off method of utility assessment. The number of years the patient has to consider is varied systematically until a point of indecision is reached. The initial number of years proposed to respondents depends on the demographic characteristics of the patient.

three subscales assess vision-related function, ocular symptoms, and environmental triggers.[3]

The Patient's Perception of Ocular Symptoms is a nine-level subjective facial expression scale used previously in dry eye studies[3] and is a component of the disease severity composite score.

The NEI VFQ-25 is a reliable 25-item questionnaire containing 12 scales: General Health, General Vision, Visual Pain, Near Vision, Distance Vision, Driving, Color Vision, Peripheral Vision, Vision-specific Social Functioning, Mental Health, Role Difficulties, and Dependency. It has been validated across a broad range of ocular disorders.[5]

Clinical and Sociodemographic Measures. Clinical measures included "walking-around" binocular Early Treatment of Diabetic Retinopathy Study visual acuity, ocular surface staining with fluorescein for the cornea and lissamine green for the conjunctiva (graded according to the Oxford scale), and tear production using Schirmer's test type-1 (without anesthesia). Sociodemographic data collected included age, race, gender, educational level, and household income.

Statistical Methods

Mean utility scores (± SD) were computed for all health states. To determine whether associations existed between patients' current dry eye utility and other health status measures, data were extracted from prospectively completed data forms, and Spearman correlation coefficients were computed. The κ statistic was used to evaluate agreement between patients and physicians regarding their assessments of disease severity. Finally, test–retest reliability was evaluated by computing intraclass correlations.

Statistical Power. The target sample size of 20 patients in each of mild, moderate, and severe dry eye groups (on the basis of physician assessment) was selected to detect an effect size of 0.4 for the utility scores, using a power of 0.80 and an α of 0.05. In this setting, an effect size of 0.4 corresponds to a difference between the largest and smallest group means that is approximately equal to the common standard deviation. Therefore, the chosen sample size yields adequate power to detect a mean group difference of 0.2, given an SD of approximately 0.2. This difference is clinically relevant; for example, mild angina has been shown to have a utility of 0.90, moderate angina 0.70, and severe angina 0.50.[22] For the total of 60 patients within each health state, a correlation coefficient of 0.36 would be detectable with a power of 0.80 (at an α level of 0.05).

Results

Study Population and Disposition

Fifty-seven patients with dry eye were enrolled. The mean age of this sample was 52.7 ± 13.9 years (range, 22–77). Eighty-one percent of patients were female. Sixty-one percent were white, and 39% were black. The mean number of years of education was 14.5 ± 2.8 (mean ± SD), and the mean yearly income was $49,000 ± $25,600 (mean ± SD).

Patients reporting higher utilities for binocular blindness than monocular blindness (indicating their preference for binocular blindness) or a higher utility for severe dry eye requiring surgery than for asymptomatic dry eye (indicating their preference for severe dry eye requiring surgery) were considered to have not understood the utility assessment process and were deemed interview failures. The interview failure (misordering rate) for the utility assessment was 29%. There were no significant predictors of interview failure as assessed by linear regression using sociodemographic factors (such as age and gender) as independent variables. Thus, assessments were based on 40 patients. Of the 40 patients, physicians classified 10 as having severe dry eye, 16 moderate dry eye, and 14 mild dry eye.

Table 1. Test-retest Reliability by Utility Assessment Method

	Time Trade-off (n = 11)	
Disease Severity Scenario	*Intraclass Correlation*	*P*
Asymptomatic dry eye	0.75	0.005
Mild dry eye	0.50	0.100
Moderate dry eye	0.43	0.161
Severe dry eye	0.73	0.007
Severe dry eye requiring surgery	0.31	0.323
Current dry eye	0.07	0.837

Study Validation

Test–retest Reliability. Overall, reliability was moderate to good for each of the dry eye states, as assessed by an analysis of test–retest reliability for a subset of patients (n = 11) who returned for a repeat utility assessment. Because of the modest sample size, only asymptomatic dry eye and severe dry eye scenarios were statistically significant (Table 1). The lowest test–retest reliability was seen for patients' self-assessment of their own condition ("current dry eye"), which was the only outcome that could theoretically change between test and retest.

Patient-physician Agreement in Designation of Dry Eye Severity. There was mild agreement between patients' self-assessment of disease severity and physician-assessed severity (κ = 0.39, 95% confidence interval, 0.18–0.61) and between self-assessed severity and disease severity composite score (κ = 0.33; 95% confidence interval, 0.13–0.52). For each disease severity, patients tended to grade their dry eye condition as less severe than that was assessed by the physician. This finding is not surprising considering that the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes concluded that subjective and clinical findings in dry eye patients do not correlate with each other.[2]

Utility Scores for Comorbidity, Blindness, and Dry Eye

Table 2 displays utility scores for comorbidity, blindness and for each dry eye severity grade. Blindness and dry eye scores are adjusted for comorbidity and scaled such that 0 = death and 1 = perfect health. Comorbidity is also scaled from death to perfect health.

For each dry eye state, utility scores ranged from 0.62 to 0.78. As expected, scores for the dry eye states made internal sense relative to the most extreme visual outcome assessed (binocular painful blindness). For example, utility for the most severe form of dry eye (requiring surgery) was 0.62 compared with 0.35 for binocular painful blindness. When patients were asked to rate their own current dry eye state, the mean utility score was the same as the mild dry eye utility score (0.81). However, the reported values ranged from 0.16 to 0.97.

Utility Loss Solely Attributable to Dry Eye

The lost utilities ("dysutility") caused by each blindness and dry eye state are presented in Table 3. As expected, there was modest condition-specific loss of utility for the mildest dry eye conditions (0.07), whereas the greatest loss of utility occurred with binocular blindness (0.52). Dry eye–specific utility loss because of the pa-

Table 2. Utility Assessments of Ocular Conditions and Comorbidities

	Time Trade-off Utility Score (n = 43)								
	Comorbidity in the Absence of Dry Eye	*Monocular Painful Blindness*	*Binocular Painful Blindness*	*Asymptomatic Dry Eye*	*Mild Dry Eye*	*Moderate Dry Eye*	*Severe Dry Eye*	*Severe Dry Eye Requiring Surgery*	*Current Dry Eye*
Mean	0.88	0.64	0.35	0.78	0.81	0.78	0.72	0.62	0.81
SD	0.14	0.29	0.31	0.23	0.18	0.19	0.23	0.26	0.19
Median	0.94	0.74	0.33	0.86	0.85	0.82	0.77	0.68	0.85

Scale: 0 = death to 1 = perfect health.
SD = standard deviation.

tients' current dry eye status (0.07) was on the average comparable to mild dry eye.

Association Between Current Dry Eye Utility Scores and Other Health Measures

In general, worsening utility scores for current dry eye correlated with worsening scores on the health status measures. The magnitude of correlation was generally mild. Unadjusted utilities for current dry eye correlated significantly with the ocular symptoms subscale of the OSDI, the bodily pain and role-emotional subscales of the SF-36, as well as the distance acuity and composite scores of the NEI VFQ (all $P \leq 0.048$) (Table 4). For adjusted utilities, significant associations were seen with the physical functioning, role physical, bodily pain, and vitality subscales, and the physical component summary score of the SF-36 (all $P \leq 0.045$), and also with the NEI VFQ composite score ($P = 0.037$).

Comparison of Utilities Between Dry Eye and Other Diseases

Table 5 compares our utility scores with other medical conditions reported on a scale of 0 = death to 1 = perfect health. Although all utilities listed were anchored on this policy scale, only some of these explicitly incorporated medical comorbidities as we have done. Those studies that explicitly reported comorbidity adjustments are denoted with asterisks in Table 5. Because of the possible differences in method, some caution should be exercised when making direct comparisons.

Mild dry eye requiring only intermittent treatment was the dry eye state resulting in the least dysutility (utility = 0.81). This level of dysutility is greater than that experienced by patients with mild psoriasis (utility = 0.89). The comorbidity-adjusted utility for moderate dry eye (0.78) was in the range of that reported for moderate angina (0.75), which was also comorbidity-adjusted. Severe dry eye and severe dry eye requiring tarsorrhaphy were associated with more dramatic reductions in utility (0.72 and 0.62, respectively). This is in the range of utilities reported by patients with class III/IV angina (comorbidity-adjusted utility = 0.71) and is worse than the utility for disabling hip fracture (0.65). Dry eye requiring tarsorrhaphy had even lower utility than monocular painful blindness (0.64). Conditions producing more dysutility than the most severe form of dry eye included moderate and major stroke, complete blindness, and AIDS. As a control, the utility calculated in this study for binocular painful blindness (0.35) was found to be similar to that seen in a previous study examining complete blindness (0.33).[23]

Discussion

To our knowledge, this is the first report of utilities for dry eye disease. We estimated the mean utility loss of severe dry eye in the absence of comorbidities to be 0.16 by the TTO method (Table 3). The interpretation of this lost utility is that patients expecting to live 10 more years would give up, on average, 1.6 years of that time to be rid of severe dry eye. This loss of utility is similar to that reported for moderate to severe (class III/IV) angina.[19] Less severe dry eye problems might carry a quality-of-life impact greater than that of mild chronic psoriasis. Even moderate dry eye yields comorbidity-adjusted utility scores and lost utility comparable to moderate angina (calculated from references 7 and 19. This suggests that effective treatments for dry eye disease can be expected to restore patient benefits of a magnitude comparable to the benefits produced by treatment for angina.

Numerous methods are available to measure utility. TTO

Table 3. Lost Utility Caused Solely by Ocular Condition

	Time Trade-off Lost Utility* (n = 43)							
	Monocular Painful Blindness	*Binocular Painful Blindness*	*Asymptomatic Dry Eye*	*Mild Dry Eye*	*Moderate Dry Eye*	*Severe Dry Eye*	*Severe Dry Eye Requiring Surgery*	*Current Dry Eye*
Mean	0.24	0.52	0.10	0.07	0.10	0.16	0.26	0.07
SD	0.22	0.29	0.16	0.07	0.10	0.14	0.20	0.07
Median	0.16	0.49	0.03	0.04	0.07	0.12	0.19	0.04

Scale: 0 = No lost utility; 1 = utility loss equivalent to the difference between perfect health and death.
*Lost utility = (Utility of comorbidities alone)-(Utility of ocular condition adjusted for comorbidities).

Table 4. Correlation of Unadjusted and Comorbidity-adjusted Current Dry Eye Utility Scores With Other Health Measures

	Time Trade-off (n = 43)			
	Unadjusted		*Adjusted*	
	ρ	*P*	ρ	*P*
OSDI				
Vision	−0.17	0.298	−0.14	0.377
Environmental triggers	−0.12	0.447	0.01	0.931
Ocular symptoms	−0.31	0.048*	−0.21	0.186
Total	−0.16	0.326	−0.08	0.632
SF-36				
Physical functioning	0.29	0.060	0.36	0.018*
Role limitation/physical	0.30	0.057	0.35	0.024*
Bodily pain	0.33	0.035*	0.32	0.037*
General health	0.16	0.310	0.15	0.348
Vitality	0.19	0.241	0.33	0.033*
Social functioning	0.27	0.084	0.26	0.103
Role-emotional	0.32	0.036*	0.24	0.125
Mental health	0.27	0.086	0.19	0.241
Physical component summary	0.30	0.056	0.31	0.045*
Mental component summary	0.27	0.084	0.16	0.315
NEI VFQ-25				
General health	0.12	0.453	0.25	0.112
General vision	0.16	0.327	0.21	0.173
Ocular pain	0.09	0.594	0.09	0.579
Near vision	0.24	0.122	0.24	0.127
Distance acuity	0.31	0.047*	0.25	0.110
Social functioning	0.17	0.273	0.19	0.232
Mental health	0.18	0.253	0.17	0.291
Role difficulties	0.28	0.078	0.30	0.056
Dependency	0.19	0.234	0.15	0.350
Driving	0.26	0.106	0.15	0.342
Color vision	0.22	0.166	0.28	0.070
Peripheral vision	0.02	0.922	0.24	0.130
NEI VFQ-25 composite	0.33	0.036*	0.32	0.037*

*$P \leq 0.05$.
OSDI = Ocular Surface Disease Index.

incorporates the quantity of life directly into the utility measure, which some believe makes this a preferred measure[24]; however, others have argued that, because the years given up are at the end of life, this could lead to an upward bias.[12] Perhaps the most important consideration is that comparisons across medical conditions should be made only using similar utility assessment methods and on similar scales.

TTO utilities had only modest correlations with the other health status measures. This was expected, because TTO requires patients to trade years of life, which depends in part on one's degree of risk aversion. The OSDI, NEI VFQ, and SF-36 require no such trade-offs and are not related to the respondent's risk tolerance. In general, unadjusted scores, which did not incorporate comorbidity, correlated better with the vision-related subscales, such as the ocular symptoms subscale of the OSDI and the distance acuity subscale of the NEI VFQ, whereas comorbidity-adjusted utility scores correlated better with global health status measures. Although current dry eye utility significantly correlated with NEI VFQ-25 composite score, the NEI VFQ-25 is not an adequate replacement for the TTO assay, because it is not a preference-based measure. Furthermore, the NEI VFQ-25 composite score is an unweighted average of the individual components and is not as theoretically valid as the TTO assay. Nonetheless, it is interesting to note that they correlate, underscoring how utility measures are important for measuring the way patients value their health state.

Several observations support the validity of our results. First, our utilities for monocular and binocular blindness are comparable with previously reported results.[9,23] Utilities for dry eye were acceptably reliable on the basis of test–retest intraclass correlations (the lowest reliability was seen for patients' self-assessment of their own condition, consistent with the fluctuations that patients with dry eye have with their symptoms). Moreover, the correlations of unadjusted and comorbidity-adjusted utility scores with other health status measures were in the expected direction for each health measure.

Although we specified "painful" blindness instead of blindness in our scenarios (because dry eye has painful symptoms), this did not result in any reduction in utility scores as might have been expected. It might be that our patients were more risk-averse compared with previously reported populations, or perhaps the marginal dysutility of "painful" in the presence of blindness was perceived as insignificant. Notwithstanding this, our utilities for blindness are strikingly similar to other reports.[9,23]

Some of our observations reflect the well-known complexity of utility assessment analysis and the multiple etiologies of dry eye disease. For example, our rate of misordered data was comparable to previous reports for utilities by TTO.[7] Although a high failure rate has the potential to bias the data, there were no significant predictors of failure rate in our analysis, indicating impartiality. The failure rate might have been lower had we used a selected patient group rather than consecutive enrollment. Also, physician-patient agreement on disease severity was weak, underscoring the differences between patient and physician perceptions of symptoms, and is consistent with the lack of correlation between dry eye symptoms and clinical signs.[2]

We did observe variability in dry eye utilities, as has been reported with utility assessments for other diseases.[7] As a result, it should be cautioned that our utilities might not apply to individual patients; however, from a societal prospective, these estimates (and particularly their trends) seem reasonable given the comparable results with previous reports for blindness.[9,23]

Increasing severity of dry eye from the asymptomatic dry eye to moderate dry eye range did not result in markedly lower mean utilities. For example, TTO utilities were higher for asymptomatic dry eye than for mild dry eye. However, the mean TTO utilities declined as the severity of dry eye increased across the entire spectrum of disease, consistent with our expectations.

Finally, although some analysts recommend assessing utilities from patients not affected with the medical condition of interest (to capture the societal perspective),[22] we desired to maximize the relevance of responses and therefore deliberately chose to sample patients with dry eye. This population also permitted us to correlate patients' utility

Table 5. Utility of Dry Eye Compared with Other Health States

Health State	Medical Condition of Subjects	Mean Utility Time Trade-off	Data Source
Treatment with warfarin	Atrial fibrillation	0.98	25
Mild psoriasis	Psoriasis	0.89	15
Mild dry eye*	Dry eye	0.81	This study
Asymptomatic dry eye*	Dry eye	0.78	This study
Moderate dry eye*	Dry eye	0.78	This study
Moderate angina*	Angina	0.75†	7, 19
Severe dry eye*	Dry eye	0.72	This study
Class III/IV angina*	Angina	0.71	19
Disabling hip fracture	Hip fracture	0.65	17
Monocular painful blindness*	Dry eye	0.64	This study
Severe dry eye with tarsorrhaphy*	Dry eye	0.62	This study
Moderate stroke	Atrial fibrillation	0.39	25
Binocular painful blindness*	Dry eye	0.35	This study
Complete blindness	Cataract	0.33	23
AIDS	HIV	0.21	26
Major stroke	Atrial fibrillation	0.11	25

*Comorbidity explicitly incorporated in utility.
†Calculated from data presented in both articles.

assessments with other clinical and vision-related quality-of-life measures among patients with the disease.

In summary, all severities of dry eye disease reduced quality of life, with severe dry eye resulting in lost utility comparable to that reported for moderate to severe (class III/IV) angina, underscoring the seriousness with which patients with dry eye view their disease. This substantial lost utility represents an opportunity for therapeutic interventions, and these results provide the basis for rigorous cost-effectiveness analyses for dry eye disease.

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EXHIBIT H

THE 2002 GALLUP STUDY OF DRY EYE SUFFERERS

Summary Volume

- Eight in ten dry eye sufferers (79%) agree that if left untreated, dry eye can lead to more serious eye problems. Despite this widespread agreement, six in ten (61%) say they don't treat their dry eye as regularly as they should.

- Three in four (74%) wish there was a more effective treatment for their dry eye, yet nearly as many (69%) say they are satisfied with the treatment being used. However, it should be noted that almost twice as many strongly agree that they wish there was something more effective than are satisfied with the current treatment (34% vs. 19%).

- A majority of sufferers take their dry eye problem seriously as only one in three (35%) agree *"dry eyes are no big deal"*.

- Fewer than four in ten (36%) feel their dry eye problem might be a symptom of another health problem.

The Question: *Please indicate the extent to which you agree or disagree with each of the following statements. (Q. 30)*

ATTITUDES TOWARD DRY EYE

	Agree Strongly %	Agree Somewhat %	Disagree Somewhat %	Disagree Strongly %	Don't Know %	Total %
You can never be too careful when it comes to eye health.	73	22	4	0	1	100
If left untreated, dry eye can lead to more serious eye problems.	31	48	18	2	1	100
I wish there was something more effective to treat my dry eye.	34	40	19	5	2	100
I am satisfied with the dry eye treatment I am using.	19	50	21	8	2	100
Dry eyes are an inevitable part of aging.	14	53	26	6	1	100
I don't treat my dry eye as regularly as I should.	13	48	23	14	2	100
I am worried my dry eye is a symptom of another health problem.	10	26	37	25	2	100
Dry eyes are no big deal.	6	29	32	31	2	100

(n=501)

IMPORTANCE OF ATTRIBUTES IN BRAND PURCHASE DECISION

- A doctor's recommendation (85%) is the attribute most likely to be rated very important in the brand purchase decision of eye ointment or gel. Majorities also assign very important ratings to a product that is long-lasting (73%) or fast-acting (66%).

- Substantially smaller proportions rate as very important the brand reputation (40%) or price (31%).

	Users of Ointment/Gel					
	Very Important	Somewhat Important	Not Very Important	Not At All Important	Don't Know	Total
	%	%	%	%	%	%
Physician recommended	85	5	1	5	4	100
Long-lasting	73	14	2	2	9	100
Fast-acting	66	17	4	2	11	100
Brand reputation	40	23	12	10	15	100
Price	31	23	32	1	13	100

(n=47)*

* *Sample size too small for reliable statistical analysis.*

The Question: *How important are the following attributes in your decision of what brand of eye ointment or gel to purchase? (Q. 29)*

EXHIBIT I

Adv Exp Med Biol
1998;438:643-51.

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A UNIFIED THEORY OF THE ROLE OF THE OCULAR SURFACE IN DRY EYE

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1. INTRODUCTION

Dry eye symptoms arise from a series of etiologies and are manifest in different patients with varying severity. The National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes, under the chairmanship of Dr. Michael A. Lemp, defined specific subtypes of dry eye in order to standardize clinical tests used in diagnosis and design of clinical studies.[1] The use of artificial tears is palliative at best, resulting in a reduction of ocular surface eyelid shear forces and some symptomatic relief. Future research should focus on mechanistic endpoints. What causative factor(s) initiates the sequence of events resulting in the clinical symptoms suffered by the patient?

This review emphasizes observations that the ocular surface (cornea, conjunctiva, accessory lacrimal glands, and meibomian glands), the main lacrimal gland, and the interconnecting reflexive innervation compose a "functional unit" (Fig. 1) whose parts act together as a servomechanism and not in isolation. In the normal individual, when afferent nerves of the ocular surface are stimulated, a reflex results in immediate blinking, withdrawal of the head, and secretion of copious amounts of reflex tears from the main lacrimal gland. These tears contain proteins, mucin, and water. Similarly, in people who face chronic ocular surface irritation due to environmental factors (contact lens, low humidity, wind, etc.), there is chronic stimulation of the lacrimal gland resulting in secretion of "sup-

Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2
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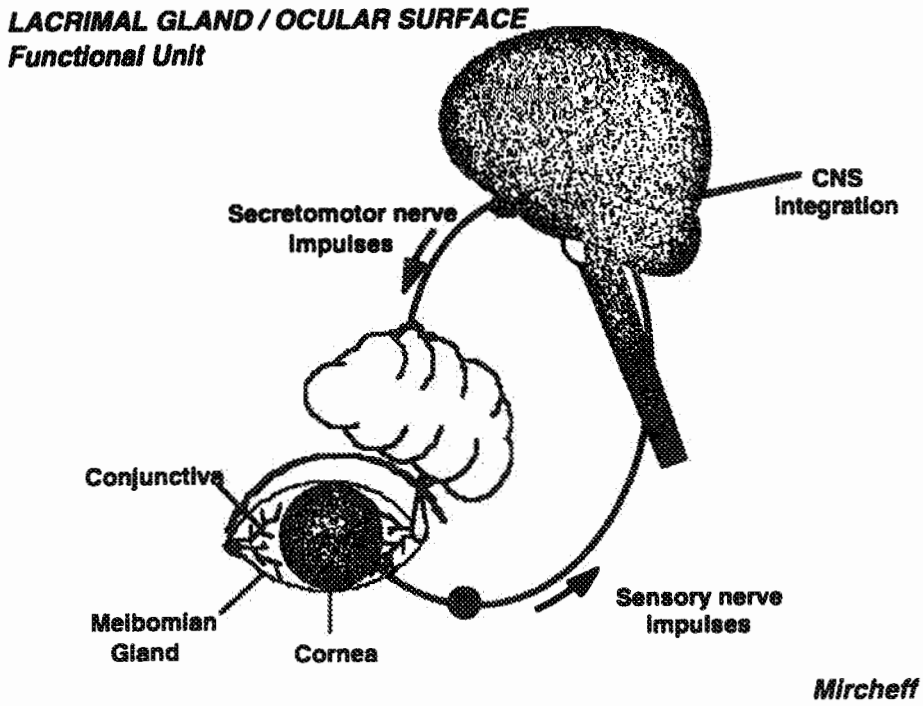

Figure 1. The functional unit comprising the ocular surface, the main lacrimal gland, and the interconnecting innervation.

portive" tears that can maintain and repair the ocular surface. In individuals suffering from dry eye, however, chronic inflammation of the ocular surface as well as of the lacrimal glands can be detected.

This "chronic" inflammation results in inflammatory cytokine secretion from the main lacrimal gland as well as the ocular surface that may interrupt both afferent and efferent arcs of the reflex and therefore impair function. The result of this pathology is a constant ocular surface irritation, which in its most severe form propagates a debilitating disease progression resulting in an inability of the patient to function normally at home or in the workplace.

The alterations in each component of the ocular surface/lacrimal gland reflex will be described.

2. OCULAR SURFACE

The ocular surface is challenged by the shear force across its surface due to blinking,[2] air currents, low humidity-induced desiccation, and foreign bodies (including contact lenses). Additionally, the ocular surface is confronted with several types of bacteria as well as viruses. The ocular surface in normal individuals remains intact and is able to repair the damage produced by these constant insults. Pflugfelder et al.[3] have shown, that diagnostic dyes, rose bengal and fluorescein, do not stain normal conjunctiva or cornea. Nelson et al.,[4] using impression cytology, however have indicated that some transient ab-

normalities can be found in clinically normal conjunctiva of people living in challenging environments. Patients with Sjögren's syndrome, who demonstrate a severe lack of aqueous tears, stain abundantly in the exposure zone.[4] In normal individuals, minor traumas, such as those already described, are rapidly healed and pose no chronic threat to the ocular surface. This is possibly due to the presence of a trophic surface environment consisting of a normal, non-inflammatory tear film. The tears in the normal individual may vary in quantity. It appears that a chronic alteration in nerve stimulation of the lacrimal gland in a dry eye individual results in inflammation and lymphocytic infiltration of the lacrimal glands. This results in secretion of diminished and altered tears that contain inflammatory cytokines, resulting in an abnormal ocular surface epithelium. The conjunctival and corneal epithelia have also been demonstrated to be competent to secrete IL-1α, TNF-α, IL-6, and IL-8.[5] The question then becomes, what conditions result in the inability of the ocular surface and the lacrimal glands to respond normally to chronic environmental challenges? Although this has not been resolved, several studies have indicated that a dramatic loss in systemic androgens found in a major target population, the peri- and post-menopausal female, results in a loss of support for lacrimal secretory function and production of an anti-inflammatory environment.[6,7]

3. CONJUNCTIVA

The conjunctiva covers the entire ocular surface outside of the cornea. Its surface is composed of a stratified mucus-secreting epithelium and a population of goblet cells also responsible for the mucus secretion. Mucus is one of the main defense mechanisms against various microtrauma. Shear forces applied during blinking (12–15/min) can cause significant trauma to the non-lubricated ocular surface.[2] If superficial trauma is induced by placing a Schirmer test strip or impression cytology membrane on the conjunctival surface, the eye will stain with rose bengal. In the normal eye, staining will no longer be observed after 24 h, indicating that a reparative process actively restores the normal surface barrier. Pflugfelder et al. (personal communications) have developed a model of conjunctival responses to microtrauma in the rabbit using nitrocellulose membranes to remove the superficial two cell layers. Then healing and cellular wound healing behavior are followed. An increase in epithelial proliferation was detected within 1 h and remained elevated for 3 days. Abnormal patterns of expression of various cell markers were detected for 1 week. A marker for basal epithelial cells, cytokeratin 14, was expressed throughout the entire epithelium,[8] and the number of cells staining for the presence of conjunctival mucin was reduced.[9] Increases in the concentrations of mRNA for inflammatory cytokines such as TNF-α, IL1-α, and IL-8 were also detected within conjunctival epithelial cells at the site of the microtrauma.[10] This phenomenon is important in part because of the conjunctival squamous metaplasia seen in moderate to severe dry eye as well as in Sjögren's syndrome. This response is seen as chronic wound healing due to the constant motion of the upper eyelid shear forces generated during blinking. Cytokine synthesis is then initiated in the traumatized corneal and conjunctival epithelium, as well as cytokines present in the lacrimal secretions, in an individual with an unsupported ocular surface (Fig. 1). In Sjögren's syndrome patients, T-cell infiltration of the conjunctiva has been found in both the epithelium and stroma.[11,12] Increased levels of IL-1α, TNF-α, IL-6, IL-8, and IL-10 have been found in the conjunctival epithelium of these patients when compared to control.[5,13] These patients, for the most part, also demonstrated expression of immune activation markers HLA-DR and ICAM-1.[5] The immunomodulatory drug cyclosporine,[13] as well as steroids,

have been found to reduce ocular surface rose bengal staining. Additionally, studies in the dry eye dog model have demonstrated that cyclosporine A eliminates both the conjunctival and lacrimal gland lymphocytic infiltrates. [4]

Alterations in the conjunctiva, such as those mentioned, occur as increased tear film abnormalities in people with keratoconjunctivitis sicca (KCS). A chronic inflammatory environment on the ocular surface results in pathologic alterations of the conjunctival epithelium known as squamous metaplasia.[3,15] A decrease in tear fluid secretion has been correlated with an increase in conjunctival rose bengal staining.[4] Patients with Sjögren's syndrome, who are unable to tear even in response to stimulation of the nasal mucosa,[16] have very severe ocular surface irritation. Patients with a decrease in lacrimation also have a decrease in various proteins such as lactoferrin and lysozyme.[17,18] Several other proteins, secreted in tears, that may be trophic to the ocular surface as well as providing an anti-inflammatory environment, are also being investigated.[13,17] It is reasonable to assume that in situations where these proteins are diminished, a pathogenic environment will exist in the ocular surface.

In many types of dry eye, in particular those associated with systemic signs of autoimmune disease, the lacrimal gland becomes infiltrated with lymphocytes. These inflammatory cells adversely affect the function of the lacrimal gland, resulting in altered tear composition and compromise of the ocular surface. The initial glandular dysfunction, however, is most probably caused by a "disconnect" at the neural/glandular interface in the perivascular region. Interruption of the neural signal at this juncture is probably part of the same mechanism that initiates the migration and proliferation of lymphocytes in the lacrimal gland and conjunctiva.

4. OCULAR SURFACE INNERVATION

The ocular surface is exquisitely innervated, with the cornea having a density of free nerve endings approximately 60X that of tooth pulp. Corneal sensation is very acute and is centrally processed and interpreted solely as pain. The conjunctiva does not transmit as acute sensations as does the cornea and is known to feel itch as well as some temperature discrimination. It is well known that corneal stimulation results in a rapid reflex including immediate blinking, profuse reflex tearing, and withdrawal of the head. The neural pathway for this reflex as well as normal tearing have been partially elucidated (Fig. 2). Sensory (afferent) traffic from the cornea and conjunctiva travels down the ophthalmic branch (1) of the trigeminal nerve (V) through the trigeminal ganglion into the spinal trigeminal nucleus located in the brainstem. The initial synapse occurs in this nucleus, and neurons then travel up to the midbrain (pons), or the preganglionic sympathetic neurons in the spinal cord and then the superior cervical ganglion, located in the paravertebral sympathetic chain. Efferent fibers from the pons extend, via the facial (VII) nerve, to the pterygopalatine ganglion located adjacent to the orbit, where they again synapse and then send fibers to the lacrimal gland where they influence the secretomotor function (modulation of water and protein transport). Sympathetic fibers from the superior cervical ganglion also enter the lacrimal gland. Schafer et al.[19] have indicated that parasympathetic neural transmission can be inhibited by cytokines. Therefore, the pro-inflammatory cytokines such as are found in the lacrimal and salivary gland biopsies of patients with Sjögren's syndrome may inhibit neural stimulation of these target tissues.

It is important to note that the control of accessory lacrimal glandular secretion as well as conjunctival goblet cell secretion is only now being investigated. Work by Seiffert

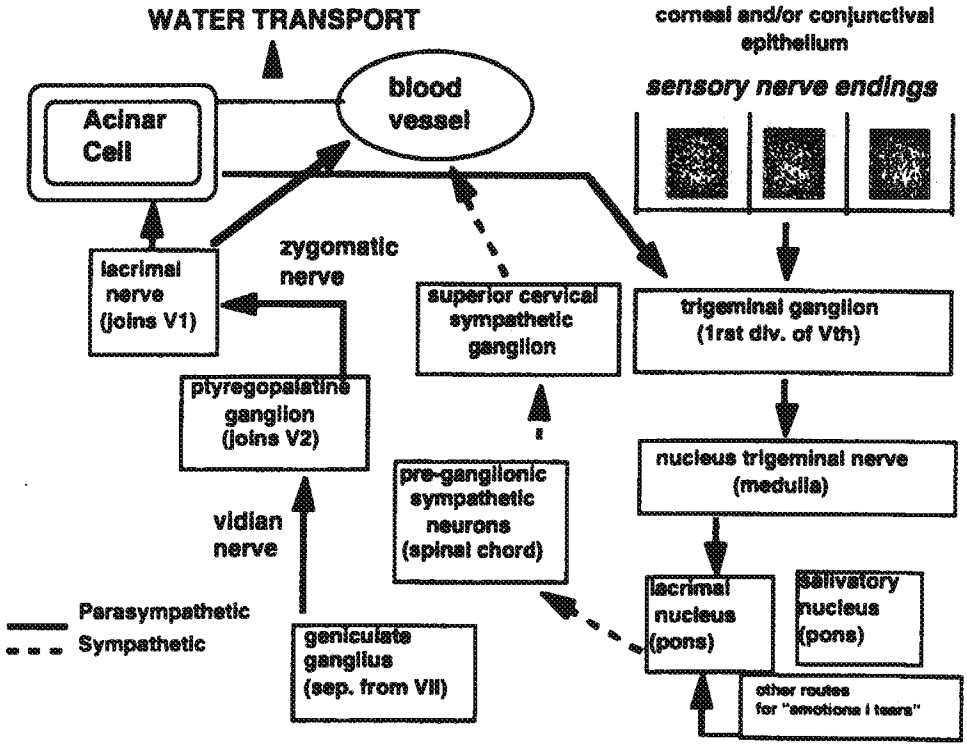

Figure 2. Afferent and efferent paths of lacrimal gland innervation for stimulation of tear flow.

et al.,[20] has demonstrated that the accessory glands are innervated, and Dartt et al.,[21] have also shown that the conjunctival goblet cells are innervated and respond to the presence of vasoactive intestinal peptide (VIP).

5. LACRIMAL GLAND

The lacrimal glands sit at the other end of the neural reflex. The main lacrimal gland resides just superior and temporal to the ocular globe. The accessory glands of Wolfring and Krause reside with the superior bulbar conjunctiva and the upper lid respectively. Although the etiology of dry eye is believed to be multifactorial and can be related to deficiencies in any of the three layers of the tear film, the major cause in Sjögren's syndrome has been reported to be a deficiency in aqueous tear production from the main and accessory lacrimal glands.[1,7] As in the salivary glands of patients with Sjögren's syndrome, as well as the conjunctiva in dogs with KCS,[14] the lacrimal glands of patients with immune-related dry eye have been found to be progressively infiltrated with lymphocytes. Immunohistochemical studies have demonstrated that these infiltrates consist primarily of CD4+ T cells and B cells.[22,23] Classically, this type of lymphocytic accumulation in the interstitium of the lacrimal or salivary gland is thought to result in immune-associated destruction of the epithelial cells in the target tissues, reduce aqueous tear secretion, and subsequently cause dry eye. The possible mechanisms are currently under investigation and discussion. The accumulated evidence indicates that the epithelial cells in the lacrimal and salivary

tissues have the potential to be antigen-presenting cells. In vitro, the lacrimal acinar cells have shown the ability to express MHC II following carbachol induction.[24] In vivo, acinar cells in the salivary gland of patients and the lacrimal gland of MRL/lpr mouse model of Sjögren's syndrome strongly express class II antigens.[5,25,26] Additionally, a recent study using PCR-single-strand conformation polymorphism (SSCP) showed that some infiltrating T cells in both lacrimal and salivary glands of Sjögren's patients recognize the shared epitopes on autoantigens, suggesting the importance of restricted epitopes of common autoantigens in the initiation of Sjögren's syndrome.[27] Therefore, it is reasonable to propose that the epithelial cells in inflamed lacrimal or salivary tissues are able to present autoantigens to the cell surface receptors such as T cell antigen receptors. The activated T cells can then secrete inflammatory cytokines such as IL-1β, IL-2, IFN-γ, and TNF-α, which may contribute to a continued local autoimmune stimulation and result in infiltration and proliferation of migrating T-cells within the glands, which, left unchecked, would result in glandular destruction.[28–30] Additionally, these pro-inflammatory cytokines can inhibit neural transmission of parasympathetic pathways and subsequently suppress neural stimulation of the lacrimal gland.[19]

It has become clear that lacrimal gland function is significantly influenced by sex hormones.[31,32] Among these actions discovered during the past decade, androgen has been found to exert essential and specific effects on maintaining the normal glandular function as well as suppressing the inflammation in the lacrimal gland of normal and autoimmune animal models.[32–37] This unique capacity of androgens is initiated through its specific binding to receptors in the acinar nuclei of the lacrimal gland and, in turn, lead to an altered expression of various cytokines and proto-oncogenes in these lacrimal gland epithelial cells.[7,38] The immmunosuppressive activity of androgens in lacrimal gland during Sjögren's syndrome is proposed to be attributed to its ability to induce the accumulation of anti-inflammatory cytokines such as TGF-β.[7,39] Given the critical role that androgen plays in many aspects of lacrimal gland, from anatomy to molecular modulation, it has been hypothesized that a decrease in androgen level below a certain threshold may result in lacrimal atrophy.[6] Apoptosis in the plasma cells of the lacrimal gland interstitium was detected 4 h following withdrawal of androgen in ovariectomized rabbits with atrophic and necrotic changes in the acinar cells occurring over the ensuing several days.[37] The resulting apoptotic fragments are also suggested to be a source of potential autoantigens and could be subsequently presented either by interstitial antigen-presenting cells or acinar cells to CD4 cell antigen receptors to initiate the autoimmune response. Our recent study in KCS dogs indicated that apoptosis plays an important role in dry eye pathogenesis. The data suggest that both the elevated epithelial cell apoptosis and the suppressed lymphocytic apoptosis in the lacrimal and conjunctival tissues of KCS dogs may be involved in the dry eye mechanisms.[40]

6. SUMMARY

It is our belief that the pathology of dry eye occurs when systemic androgen levels fall below the threshold necessary for support of secretory function and generation of an anti-inflammatory environment (Fig. 3). When this occurs, both the lacrimal gland and the ocular surface become irritated and inflamed, and they secrete cytokines that interfere with the normal neural connections that drive the tearing reflex. This leaves the lacrimal gland in an isolated condition, perhaps exacerbating atrophic alterations of the glandular tissue. These changes allow for antigen presentation at the surface of the lacrimal acinar

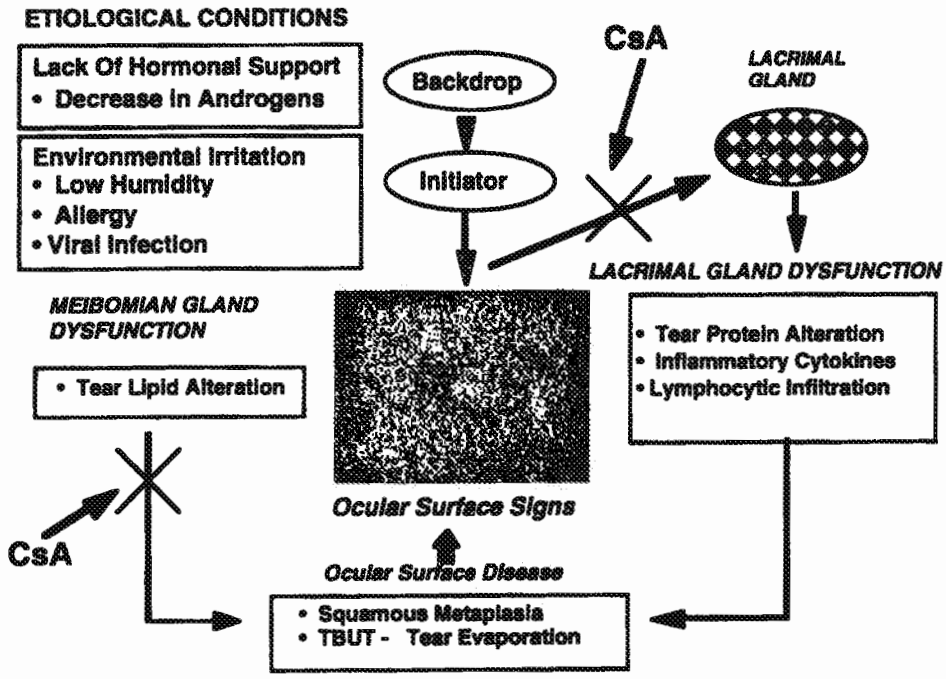

Figure 3. Proposed model of etiology and pathogenesis of dry eye. Included are etiologic factors (background, initiator) and the sequence of events resulting in alterations of the ocular surface. Possible therapeutic interventions (cyclosporine, androgens) are indicated.

cells and increase lymphocytic infiltration of the gland. A similar series of events may be occurring on the ocular surface.

From this hypothesis we conclude:

1. The ocular surface, lacrimal gland, and interconnecting innervation act as an integrated servo-mechanism.
2. Once the lacrimal gland loses its androgen support, it is subject to immune/ neurally mediated dysfunction.
3. The ocular surface is an appropriate target for dry eye therapeutics.

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EXHIBIT J

Integrating Restasis into the Management of Dry Eye

Stephen C. Pflugfelder, MD

The approval of cyclosporin emulsion for treatment of the inflammatory component of dry eye by the US Food and Drug Administration in December 2002 represents a major paradigm shift in the treatment of dry eye and in our understanding of its pathogenesis. There is mounting evidence from basic and clinical research demonstrating that inflammation is both a cause and consequence of dry eye. Certain inflammatory mediators, such as interleukin 1 have been found to cause lacrimal dysfunction though functional paralysis of the secretory epithelia,[1] whereas others (eg, interferon-γ and tumor necrosis factor-α) may interfere with normal differentiation and promote apoptosis of lacrimal gland and ocular surface epithelial cells.[2,3]

Topical cyclosporine emulsion has been found to have a salutary effect on ocular irritation symptoms, tear production, and ocular surface epithelial disease in patients with keratoconjunctivitis sicca.[4] Several mechanisms of action of cyclosporine emulsion have been identified, including inhibition of epithelial apoptosis and cytokine production by the activated T lymphocytes that infiltrate the conjunctiva in keratoconjunctivitis sicca.[5,6] T-cell infiltration of the conjunctiva has been found to be a feature of Sjögren and non-Sjögren syndrome keratoconjunctivitis sicca.[7] These T cells seem to be chemoattracted by the stressed ocular surface epithelia and once in place produce factors such as IFN-γ that push differentiation of the ocular surface epithelium toward a poorly wettable skinlike pattern. These findings suggest that keratoconjunctivitis sicca is similar to psoriasis and inflammatory bowel disease, conditions where T cells have been identified to play a key role in the epithelial pathology.[8,9] The improved understanding of the pathogenesis of keratoconjunctivitis sicca, particularly the role of T cells in this process, helps to explain the observed clinical efficacy of topical cyclosporine emulsion for treatment of this condition.

How does cyclosporine emulsion fit into the armamentarium for treatment of keratoconjunctivitis sicca? An international task force held at the Wilmer Eye Institute in December 2003 proposed a treatment algorithm for treatment of dry eye based on scientific evidence and clinical experience.[10] This group categorized dry eye into 4 severity levels based on irritation symptoms, clinical signs, and diagnostic tests. Patients with level 1 severity complain of mild episodic irritation symptoms, may have an unstable tear film, mild conjunctival dye staining and no corneal epithelial disease. In level 2, patients now experience chronic irritation symptoms and show evidence of peripheral corneal epithelial disease. In level 3, the central cornea is involved and patients may develop filamentary keratitis and level 4 is blinding dry eye, such as severe Sjögren syndrome or Stevens-Johnson syndrome where the cornea may opacify or ulcerate. Therapy of level 1 disease consisted of artificial tears, elimination of offending environmental factors, or systemic medications increasing oral intake of omega-3 fatty acids. The addition of cyclosporine emulsion to these other therapies was recommended for treatment of level 2 and worse disease where the chronic nature of the disease and ocular surface epithelial changes indicates an inflammatory component. There was consensus among the group that ocular surface inflammation should be controlled before temporary or permanent punctual occlusion.

The improved understanding of the role of inflammation in the pathogenesis of dry eye raises the issue of whether cyclosporine therapy should be initiated prophylactically in patients who are at high risk for developing level 2 severity or worse disease, such as patients with Stevens-Johnson syndrome, systemic autoimmune conditions (eg, rheumatoid arthritis and systemic lupus erythematosis) or early signs of graft-versus-host disease after allogenic bone marrow transplant.[11] Early intervention may minimize the risks of developing debilitating irritation and blinding complications such as permanent goblet cell loss, stem cell deficiency, or corneal ulceration that can develop in these diseases. Additional evidence will be required to address this issue.

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EXHIBIT K

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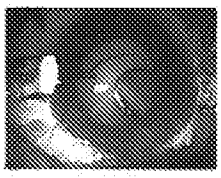
OSN EXCLUSIVES

COMPLICATIONS CONSULT

Unfolding of IOL key to glued intrascleral fixation



The surgeon needs to be aware of the 'lucky 7/ inverted C' sign and the 'upright C' sign during the process of unfolding the IOL. 33

LINDSTROM'S PERSPECTIVE

Ocular surface management critical to patient satisfaction 6

IN THE JOURNALS

Phaco with torsional or tudinal ultrasound esult in high thelial cell loss
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ICE MANAGEMENT
HE PREMIER SURGEON

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ting Highlights
New York

ing coverage starts on page 14

COVER STORY

Panel recommends treating ocular surface prior to any refractive procedure

Eighty-six percent of patients with dry eye have both meibomian gland dysfunction and aqueous deficiency, an important consideration when optimizing the corneal surface before surgery — any type of ophthalmic surgery.

Whether PRK, LASIK or cataract surgery is the scheduled procedure, the greatest risk factor for a poor outcome in refractive surgery is pre-existing dry eye, according to **Eric D. Donnenfeld, MD**, who chaired the OSN New York Dry Eye, Anti-inflammatory and Allergy Corneal Health Roundtable.

"We have taken a new approach of evaluating patients for ocular surface disease before considering any type of surgery, including cataract surgery," Donnenfeld said. "We can improve the outcomes dramatically by managing these patients."

OSN New York Corneal Health roundtable participants tackle the issues of treating aqueous deficiency as well as meibomian gland dysfunction, giving their own twists on current recommendations. Crossing specialty lines, a glaucoma specialist adds his thoughts on advances in medical management of glaucoma that trend toward minimizing the effect on the ocular surface.

Cover story starts on page 10

Marguerite B. McDonald, MD, FACS, is among authors who have published studies on the utility of a preoperative course of cyclosporine.

Retained subretinal perfluorocarbon more prevalent with smaller-gauge vitrectomy

A higher incidence of retained perfluorocarbon was found in patients who underwent 23-gauge vitrectomy rather than traditional 20-gauge repair of retinal detachment.

"After transitioning from traditional 20-gauge vitrectomy to 23-gauge vitrectomy, it appeared to me that there was an increased incidence of subretinal perfluorocarbon liquid," **Sunir J. Garg, MD**, said.

Garg retrospectively reviewed 234 retinal detachment repairs he had done over a 3-year period and found a 10.3% incidence of retained PFCL when he used the smaller-gauge instrumentation. Incidence was 2.3% in the 20-gauge cases.

"Although microincision vitrectomy is a great advance, with any new technology comes subtle changes that we might not appreciate or realize," Garg said. "I expected there might be a slightly higher rate of subretinal PFCL with 23-gauge vitrectomy, but not a 4.5-fold increase."

Reducing turbulence within the eye is the critical part of primary surgery. Garg has begun using valved 23-gauge cannulas, which create less turbulence, he said.

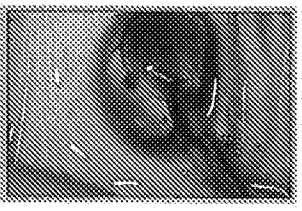
Two other options for decreasing turbulence are reducing the infusion pressure when using non-valved cannulas and clamping the infusion line when removing instruments from the eye.

A follow-up study using valved 23-gauge cannulas is currently under way.

For more on this story, see page 9.

Surgical Maneuvers: High-viscosity OVD helpful in MICS

The ophthalmic viscosurgical device aids in chamber stability and corneal protection. 8



COVER STORY

Panel recommends treating ocular surface prior to any refractive procedure

The biggest risk factor for a poor outcome in refractive surgery is pre-existing dry eye, according to a panel of experts.

"We have taken a new approach of evaluating patients for ocular surface disease before considering any type of surgery, including cataract surgery," **Eric D. Donnenfeld, MD,** OSN Cornea/External Disease Board Member, said at a panel gathered to address management of ocular surface disease. Patients who are being evaluated for LASIK and PRK overwhelmingly have preoperative dry eye, he said.

"We can improve the outcomes dramatically by managing these patients," Donnenfeld said at OSN New York during the Dry Eye, Anti-inflammatory and Allergy Corneal Health Round Table, which he chaired.

Getting started

Donnenfeld kicked off the discussion with the case of a 43-year-old myopic woman with mild to moderate dry eye. The edited round table follows; the panelists discussed off-label use of some products.

Donnenfeld: In a myopic patient with active staining of the conjunctiva and cornea and with mild to moderate dry eye, what is the best refractive procedure? Many ophthalmologists would say PRK, and others would say no treatment, as would be expected, but there are additional options.

Douglas A. Katsev, MD: If the patient is 43 years old, it is hard to put in a phakic IOL. PRK, in my experience, causes less dry eye than LASIK, but certainly maximizing the tear film and treating with all appropriate medications and heat to the lids is the most important thing to do before getting started in any direction.

Donnenfeld: How common is it to have mixed mechanism disease, that is, both meibomian gland dysfunction (MGD) and aqueous deficiency, and how would you treat it?

Marguerite B. McDonald, MD, FACS: Michael Lemp published a paper proving that 86% of the patients with dry eye have concomitant MGD.

Donnenfeld: So this is the rule. In the past, we treated one or the other. We need to think about treating both of these diseases to maximize results. Let's start by talking about aqueous-deficient dry eye. What would be your starting point for managing this patient?

Treating aqueous deficiency

Henry D. Perry, MD: I would start with non-preserved artificial tears and topical cyclosporine, which is sometimes underused in patients with mild dry eye disease. It is important in any type of chronic ocular surface disease, especially due to aqueous deficiency, to begin topical cyclosporine.

Donnenfeld: What if the patient does not want to wait 3 to 6 months for cyclosporine to hit full stride?

Perry: Then we also have nutritional supplements. Fish oil, especially omega-3, is helpful, and we can see results in as little as 2 weeks.

Donnenfeld: I like nutritional supplements as well. In our practice, we use second-generation omega-3 fish oils in which the natural triglyceride provides significantly greater DHA and EPA absorption than first-generation fish oils that have been converted with alcohol to an ethyl ester form. I believe brands such as Nordic Natural in stores and PRN in doctors' offices, which is what I use, provide much better results.

In addition, we have been adding topical corticosteroids such as loteprednol when we initiate therapy. Combination immunomodulation does great work to get these patients comfortable, and it reduces burning and stinging.

McDonald: Some experts have recommended a run of topical steroids first and then starting Restasis (cyclosporine ophthalmic emulsion 0.05%, Allergan). I start patients on both simultaneously, largely because when patients have steroids first, they never want to start cyclosporine. They do anything they can to stay on the topical steroids, which do two things: They blunt or totally eliminate the stinging that often accompanies the induction of cyclosporine therapy, and they give immediate symptomatic relief. So patients have real belief that your suggested regimen is working. And in 4 to 6 weeks, you can turn this person from a suboptimal candidate for laser surgery into a pretty good candidate.

Donnenfeld: That is the key here. You need to evaluate these patients, and if they respond, they become good candidates for LASIK or PRK. If they do not respond, then you are probably best off doing nothing. There is a new steroid that will be coming out that I think is going to be exciting for this type of case, and that is loteprednol gel, which will be available in the first quarter of 2013. I think that will provide even more ocular surface coverage and better contact time.

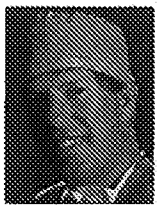
Perry: In our office, when we start topical cyclosporine, we always start a low-dose corticosteroid. Several authors have shown the efficacy of increasing the success of topical cyclosporine with low-dose loteprednol, and it has been shown by two other groups that the concomitant use of steroids is beneficial, not only in the initial treatment, but also in allowing the success of the long-term use of topical cyclosporine.

Katsev: When you are going to start cyclosporine, patients need to know that they are going to be taking this medication for 4 to 6 months. They need to communicate to me that they are willing to take it that much. I also start topical steroids, so I need commitment for 4 to 6 months and

Round table participants

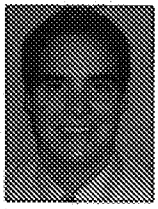

Eric D. Donnenfeld
Moderator


Richard M. Awdeh


Douglas A. Katsev


Kenneth R. Kenyon


Marguerite B. McDonald


Robert J. Noecker


Henry D. Perry

I need to know that they understand the disease.

McDonald: With loteprednol etabonate starting at the same time as cyclosporine, I prescribe four times a day for 2 weeks, twice a day for 2 weeks, and then the patient is off the loteprednol while the cyclosporine continues.

Donnenfeld: That is the Asclepius Panel recommendation.

Kenneth R. Kenyon, MD: I continue to believe that it is important to definitively diagnose aqueous-deficient dry eye by determining if the patient, in fact, has aqueous deficiency. Back in the day, we performed basic secretion Schirmer tests with topical anesthetic. Three decades later, I continue to use this same test to screen for aqueous deficiency. The notion that a patient with a basic secretion Schirmer score of perhaps 10 mm in 5 minutes has an aqueous-deficient dry eye and therefore deserves Restasis and/or punctum occlusion is simply incorrect. In such a case, other mechanisms of ocular surface disease, such as MGD, exposure or decreased corneal sensation, must be investigated.

I am sure we all have our differing views, but I will say that it is important to be clear when you are doing a pre-laser vision correction workup to have space on your diagnostic forms for both lids and tear functions. It will keep you out of trouble; it will keep you out of malpractice suits. I am certainly concurrent with everything else that has been offered about various medical and pharmaceutical therapies, but a Schirmer test tells me a heck of a lot and then allows me to decide whether to go down the route of plugs or even punctum cauterization, which after the inflammatory component of the surface is under control, is a time-honored valid therapy.

Donnenfeld: Punctal plugs work fairly well in aqueous-deficient dry eye. You want to stabilize the ocular surface first. If you want to make a patient unhappy, in my experience, put a punctal plug in someone with significant MGD. Those patients are just miserable. So, when do you start punctal plugs in these patients?

Kenyon: I have become cognizant of the notion that you do not want to create an ocular surface cesspool, as it were, by totally denying all aqueous and, hence, other toxic waste outflow. But after you get the surface in good anti-inflammatory status, then it is time to intervene with punctum occlusion, whether by a homemade "quick and dirty" 3-mm length of 5-0 chromic suture or with more extended duration intracanalicular inserts such as Oasis or semi-permanent silicone plugs. These are all variations on the theme. But first it is anti-inflammatory and then it is punctal occlusion, if you, in fact, have a true aqueous-deficient component.

Anti-inflammatories in glaucoma

Donnenfeld: Do you find that anti-inflammatory therapy, notably cyclosporine, plays a role in glaucoma management?

Robert J. Noecker, MD, MBA: Without a doubt. When you look at the demographic information, these are two diseases with parallel comorbidities. In the general population, a rough statistic for ocular surface disease in age-matched controls is around 15% vs. around 50% in the glaucoma population. The argument is that glaucoma therapy tends to make people worse.

Donnenfeld: A lot of glaucoma specialists resist the idea of early surgery, but for the corneal specialist, often the best thing to do is to get the patient off the glaucoma drops. Often, I will recommend something simple, like laser trabeculectomy or selective laser trabeculoplasty in phakic patients or an iStent (Glaukos) if the patient is having cataract surgery, to get a patient off of a glaucoma medication.

Noecker: Certainly SLT and laser interventions are easier to do. And now we have microinvasive glaucoma surgeries, which are lowering the bar in terms of not causing significant morbidity commonly associated with glaucoma surgery.

The other point is that it is an amazing time in glaucoma medical therapy because there are so many options to avoid the common preservative we talk about: benzalkonium chloride (BAK). If it is not possible from a formulary standpoint to eliminate BAK, then every new formulation has less and less BAK than the formulation had 5 or 10 years ago. You can have people on a preservative-free prostaglandin or a non-BAK alternative preservative prostaglandin. You can have them on preservative-free dorzolamide timolol. You can have them on preservative-free timolol alone. You can have alternatively preserved brimonidine. So you could do a whole treatment regimen without ever having to worry about the preservative effect. Active ingredients certainly and pH also play a role, but the preservative is the common denominator.

Donnenfeld: As a corneal specialist, if you can get patients off of these drops for a lifetime, the quality of life and the improved vision are significant.

Meibomian mechanism

Donnenfeld: Because we are talking about a mixed mechanism of ocular surface disease, let's move on to the management of MGD. What would be your first line of therapy for managing someone with MGD?

Cover story continues on page 12

POINT / COUNTER

With the emphasis on optimizing the ocular surface and minimizing preop dry eye, what is the value of the Schirmer test in particular before conducting refractive surgery?

POINT

Popularity of Schirmer test eroding


Thomas John

Ocular surface optimization should be considered an integral part and package of current day refractive surgery in order to deliver the optimal visual outcome, meet our patients' high expectations, and convert them to satisfied customers. In this endeavor there are various venues to pursue with regard to pre-refractive surgery detection of dry eyes, and one age-old test is the Schirmer test. Since its entry into this arena, Schirmer test rapidly gained popularity among clinicians, primarily driven by the fact that it is readily available, is relatively inexpensive, is easy to perform, and lacks clinically noticeable side effects. However, like everything else in life, its sustained popularity as an aqueous tear deficiency test has been slowly eroding, as reflected by one of the ASCRS surveys that reported 70% of the surgeons are not using pre-refractive surgery Schirmer test.

So why is there a change of heart toward Schirmer test? It is multifactorial, and some of the reasons may be attributed to the fact that the results can be quite variable. Based on the Schirmer test, one report showed that 17% of asymptomatic subjects would be misdiagnosed as dry eye patients. A more recent study showed that subclinical tear deficiency indicated by low Schirmer test values did not influence PRK outcomes in patients matched by age and magnitude of refractive correction.

It is important to listen to patient symptoms of dry eye, look for clinical biomicroscopic signs of dry eyes even in those asymptomatic individuals, and consider incorporating some of the newer, technology-driven dry eye tests that may be suitable in your refractive surgery practice.

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***Thomas John, MD,** is an OSN Cornea/External Disease Board Member. Disclosure: John has no relevant financial disclosures.*

COUNTER

Schirmer test still relevant


Penny Asbell

Dry eye continues to be a significant problem and a cause of dissatisfaction after laser surgery. There are a lot of reasons why these patients might have dry eyes, but the key reason is preop dry eye disease. So when we are thinking about laser, we should be thinking about preop diagnosis of dry eye disease. In a study that asked physicians what they do to evaluate patients before refractive surgery, as expected nearly 100% of physicians said they perform corneal topography, but only 30% of the physicians performed Schirmer's. We may argue that Schirmer's isn't the best dry eye test; nonetheless it is interesting to see that the physicians were not thinking about that. That's a take-home message. Let's think about it before the laser, not afterward.

Excerpted from Asbell PA, Gadaria N, Lee K-I. "The Ocular Surface and its Impact on LASIK and PRK" presented at OSN New York, Nov. 16-18, 2012.

Reference:
Solomon KD, et al. *J Cataract Refract Surg.* 2002;28(2):346-355.

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Cover story continued from page 11

Perry: The first thing is be sure of the diagnosis, as Dr. Kenyon said. I like to express the glands to get a feeling for the consistency and where we are in terms of the MGD in that particular patient. Heat is essential to melt the fats to get them flowing, and it is important that we remember that in this particular disease the change from long-chain fatty acids to free fatty acids with the inflammation leads to saponification or a soap formation. The problem is that there is too much detergent in the tears. Artificial tears can do a lot to help, and topical cyclosporine, topical steroids and nutritional supplements are also helpful. Lid hyperthermia is essential. Oral doxycycline changes the equilibrium constant from free fatty acids back to long-chain fatty acids and helps decrease the inflammation, as does topical azithromycin. Pulsed light therapy also helps in terms of heating, but there have been some disasters that occurred when the iris was fried by mistake.

Donnenfeld: I have become a big believer in nutritional supplements. What do you recommend to your patients who have MGD?

Richard M. Awdeh, MD: The increased importance of nutritional supplements is clear, both to us as a society and to us in clinic and with our patients. I will recommend that patients go on a vitamin therapy or TheraTears (Akorn) type of nutritional supplement, but additionally I ask patients to review their diet for rich foods — chocolates, cheeses, wines, caffeine, nuts — and I will ask them to modify their diet.

For these patients, I do not like putting them on an oral systemic therapy unless we get to that point, and if we do, then we will put them on oral doxycycline 100 mg two times per day for a few weeks and then switch to 100 mg daily. We ask them to take it with a snack and avoid sun exposure and ambient sun.

We have had success with topical azithromycin, again doing a staged approach, starting a low-dose steroid and then tapering the steroid down as the azithromycin has time to work.

With topical cyclosporine, there are instances when patients are not comfortable with it. We have a compounding pharmacy that creates the topical cyclosporine in different concentrations and in different vehicles, including a corn oil, for instance. We sometimes notice a good response in patients who were previously intolerant.

Kenyon: Half of my blepharitis and meibomitis patients do well simply with a warm compress for 5 minutes and erythromycin. That is traditional. Another 25% with any hint of rosacea will be knocked off with low-dose doxycycline or minocycline, which can go on benignly for years. So all this is good stuff, including LipiFlow (TearScience), but there is still a lot out there in the traditional armamentarium.

> **"We have taken a new approach of evaluating patients for ocular surface disease before considering any type of surgery."**
> — ERIC D. DONNENFELD, MD

LipiFlow expression

Donnenfeld: Consider the case of a 55-year-old patient with a long history of tired eyes, no medications, no corneal or conjunctival staining, drinks heavily, 2+ MGD, shortened tear break-up time who is treated with hot compresses, nutrition and LipiFlow. Patients who have marginally compensated ocular surfaces respond by blinking more often, and when they blink more often, they develop tired eyes. He had the therapy, the tired eyes got better, and the blinking reduced.

Kenyon: I have no proprietary interest here, but one of my practice partners, Jack V. Greiner, MD, has been doing studies for TearScience, so I have watched developments with interest. I believe LipiFlow works, but it is pricey.

Having said that, Greiner has done follow-up studies on some of his patients for more than 2 years, and this single 12-minute pulsed heat therapy does indeed unblock the glands. Whether it is by the subjective surveys such as the Ocular Surface Disease Index and the Standard Patient Evaluation of Eye Dryness, or all the objective measures, LipiFlow therapy does seem to have a protracted effect. So despite the self-pay "sticker shock" disadvantage, you can at least reassure patients that they will benefit for at least a year or perhaps longer.

McDonald: When we do hot compresses at home, most of that heat is wicked away by the lid structures, which are highly vascular. So little of the externally applied heat gets all the way back to where we want it to — the meibomian glands. But with the LipiFlow system, the heat is applied from the tarsal plate conjunctival side of the lid, so that the altered meibum becomes liquefied; then gentle pulsations start and the altered meibum is extruded. It is a much more effective way to apply heat, and to a much higher temperature — though still to a controlled and comfortable degree — than patients could ever get at home.

Tears and optimizing the surface for surgery

Donnenfeld: Consider the same patient who is going to have LASIK or PRK who had mixed mechanism ocular surface disease and is now better. Let's talk about what can be done surgically.

Literature now shows that making thin planar flaps gives better results. Bevel and side cuts provide better adhesion. Flaps can be smaller. In the old days, we were making 9.5-mm flaps for myopes. In a patient with a small pupil, you can go down to 8.1- or 8-mm flaps. You have half the surface area; half the corneal nerves are cut. There are a lot of ways for surgical modification. I do not think personally that there is now a big difference between PRK and small-flap LASIK with advanced techniques. In the old days when we made 150-µm flaps there was a big difference, but now I think PRK and LASIK are both reasonable techniques for managing these patients.

Awdeh: I agree. The key is to get the patient to baseline before surgery and to make sure that their symptoms have improved. Make sure that your objective is such that the patient is also true to the Schirmer's test and staining of the cornea.

Donnenfeld: Dr. McDonald, you wrote one of the definitive articles on using cyclosporine in these patients. How long do you continue cyclosporine after LASIK, and does it really affect the visual results?

McDonald: Yes. There are now at least five papers in the peer-reviewed literature documenting that whether you are old or young, male or female, and dry or not, you will have a better post-LASIK clinical outcome with a preop run-in of cyclosporine and using it for at least 3 months afterward. One of those papers is ours, using cyclosporine in extremely dry eye patients, who are considered very high-risk LASIK candidates. It made a big difference in the percentage of patients who achieved 20/20 uncorrected vision and in the percentage that needed an enhancement, both in favor of the cyclosporine-treated group.

Kenyon: Based on your work, I use Restasis for at least a month preop in any patient with a Schirmer test value of less than 5 mm basic secretion. I can continue it for up to 3 months postop. I always do LASIK in these patients because I think that their ocular surface is less compromised from the beginning, so the neurotrophic component of creating a LASIK flap is far offset by the need for the epithelium to regenerate in a potentially drier environment. If you do everything that we have described here to optimize the ocular surface first, then you will not get into trouble later with ocular surface difficulties, whether due to a single mechanism or a combined mechanism.

Donnenfeld: Ed Manche just published a paper in *Ophthalmology*, in which LASIK was done in one eye and PRK in the other eye, and patient healing was evaluated. There was no difference in dry eye between the two groups, and the healing was better in the LASIK group because of the problems of epithelial remodeling.

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EXHIBIT L

Article Date: 9/1/2013

Focus on Dry Eye

Restasis: 10 years after launch

The drug has found a strong niche in dry eye therapy.

By Jerry Helzner, Senior Editor

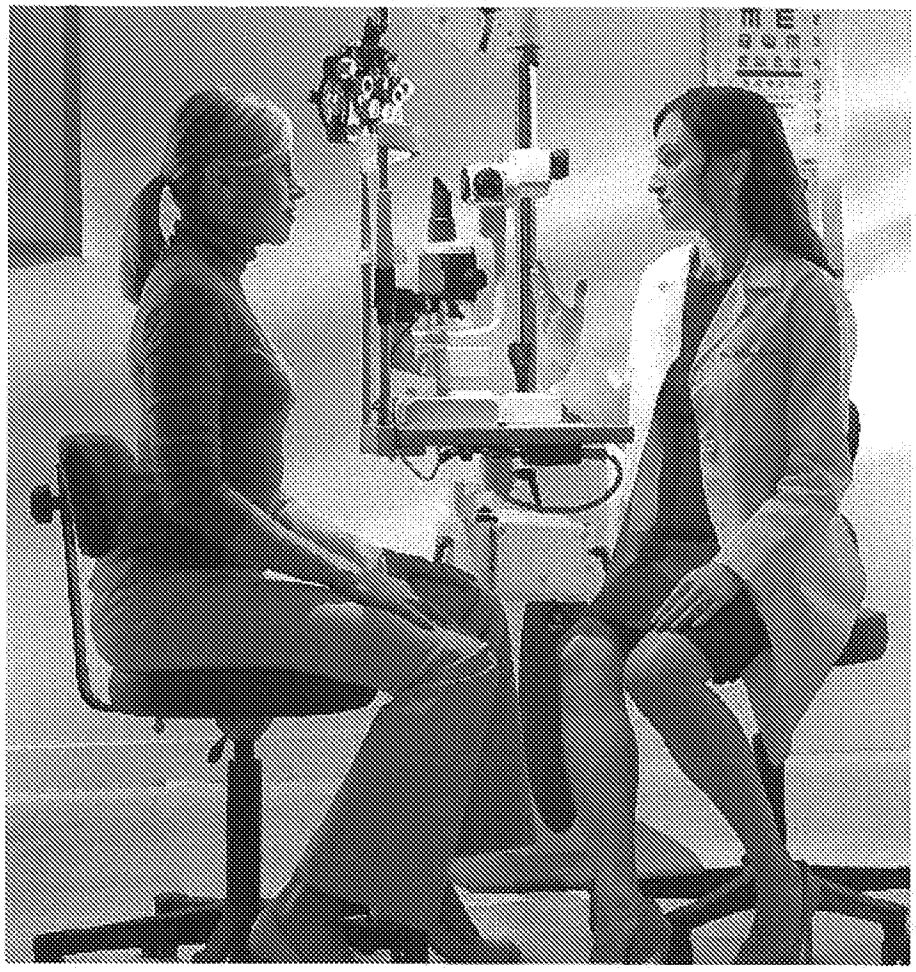
Launched by Allergan in the United States in April 2003, Restasis (cyclosporine ophthalmic emulsion 0.05%) had the advantage of being the first — and still the only — FDA-approved prescription drug for chronic dry eye disease. For people who had spent years trying to cope with their disease, primarily with oceans of artificial tears, just two drops of Restasis each day was designed to attack the underlying inflammatory characteristic of the disease and allow patients to produce more natural tears.

Sales continue strong growth

Now, a decade after it was introduced, Restasis can be deemed a success. Ophthalmologists interviewed for this article say it has earned a significant place in their overall treatment plan for combating dry eye disease. Patients worldwide have now accounted for 16 million prescriptions for the drug, translating to a compounded 40% annual sales growth, according to Allergan. In 2004, its first full year of US sales, Restasis totaled $98 million in revenues. This year, Allergan expects Restasis to record between $870 and $900 million in worldwide sales, making it the company's best-selling ophthalmic drug by far.

In the latest reported quarter, the second quarter 2013, Restasis was still growing sales by double-digits (10.5%), even though the drug has been in the marketplace for a decade. What's more, Restasis has been blessed with an ongoing marketing campaign featuring a series of television ads that focus on the endorsement of cornea specialist Alison Tendler, MD, of Vance Thompson Vision in Sioux Falls, S.D.

Given that Restasis has made a considerable impact on the treatment of dry eye disease over the past 10 years, what have ophthalmologists who treat dry eye learned about the drug during this time that allows them to use it more effectively? This article will focus on the experiences of three corneal specialists who have successfully integrated Restasis into their arsenal of dry eye treatments, two of whom actually use Restasis themselves.



A scene from one of a series of Restasis television ads featuring spokesperson Allison Tendler, MD.

THE LEARNING CURVE
Restasis needs time to work

Stephen Pflugfelder, MD, of the Cullen Eye Institute at Baylor College of Medicine in Houston, has extensive experience with Restasis, having served as an investigator in the drug's pivotal phase 3 trial. He believes Restasis came along at just the right time. "In terms of treating dry eye and ocular surface disease, prior to the introduction of Restasis, artificial tears just weren't cutting it because inflammation is a big part of the disease," he says. "Restasis has helped us to treat the inflammation."

Dr. Pflugfelder says he went through a learning curve in the use of Restasis that has helped him to be more accurate in selecting patients for whom the drug is most effective. "First, it's very important for both doctors and patients to recognize that it takes a while for Restasis to begin to work," he notes. "It could be four to six weeks and it could even be longer, but I have found that the drug's effectiveness gets better with time. It is so safe that you can use it indefinitely, which is a major advantage."

Dr. Pflugfelder says patients who produce low tear volume at baseline tend to do better on Restasis than patients who produce more of their own tears. He has also conducted in-house research that points to patients with low goblet cells as good responders to Restasis therapy. "Restasis appears to have the ability to repair goblet cells," he notes.

Can Allergan fight off generic Restasis?

If imitation is the sincerest form of flattery, than Allergan should feel quite flattered these days. As the basic patent for Restasis is set to expire in May 2014, generic drug manufacturers are salivating at the chance to get into the marketplace

with their version of what is now close to a $1-billion-a-year drug.

A generic version of Restasis may be close at hand if recent FDA draft guidance becomes a reality. In June, the federal agency proposed that human trials of generic Restasis may not be necessary if laboratory testing can demonstrate the chemical equivalence of the drugs. With that standard for approval, the timetable for a generic version could be pushed ahead by years. That fact was not lost on Allergan stockholders as the price of Allergan shares tumbled 12% the day after the FDA draft guidance was announced.

Allergan has already begun the fight to ensure that human trials are conducted for any generic version of Restasis. In a statement issued following the FDA announcement, Allergan said it believes the FDA's proposed testing method "cannot predict clinical safety and efficacy, and thus cannot be used to establish bioequivalence."

Allergan said it will provide feedback to the FDA during the 60-day comment period. The company asserts it is weighing all options in an effort to prove the FDA's proposal, if carried out, would not be in the best interests of consumers.

Two factors could work in Allergan's favor to forestall competition. First, the Restasis manufacturing process is highly complex and could delay a potential competitor's ability to make the drug. Second, an improved, next-generation Restasis would provide a competitive advantage and more years of patent protection for the improved product. Allergan is also now conducting a phase 2 clinical trial for a next-generation dry eye therapy called Restasis X. The company would not comment on a possible timetable for approval of the next-generation product.

Short-course steroids can help

Because Restasis takes a while to begin to work, Dr. Pflugfelder often starts his dry eye patients with a short course of topical steroids, which lasts about a month. "The topical steroid does two things," he says. "It provides earlier relief for the patient and it mitigates the burning or stinging sensation that many patients feel when they begin Restasis."

TREATMENT PLANS AND TIPS
Dr. Pflugfelder's treatment plan

The cornea specialists interviewed for this article agree that Restasis must be part of an overall treatment plan. It is not a panacea that can stand on its own. "No single drug can work for all patients," says Dr. Pflugfelder. "An overall treatment plan for dry eye disease could include one or more of the following: supplements such as fish oil, the antibiotic anti-inflammatory doxycycline, punctal plugs and the antibiotic AzaSite (azithromycin, InSite Vision, Alameda. Calif.)."

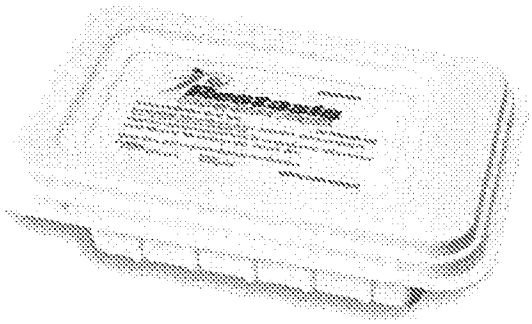
About 80% of the patients to whom he prescribes the drug do well on it, Dr. Pflugfelder says. "I have patients who have gone from debilitating dry eye to functioning very well. Another benefit is that these patients can decrease the use of artificial tears."

The doctor is also a patient

Christopher Starr, MD, FACS, of New York-Presbyterian Hospital, Weill Cornell Medical Center in New York, was just completing his fellowship training when Restasis was launched in the United States a decade ago. "I have had the benefit of being able to prescribe Restasis for my entire career," he notes. "I consider it the foundation of my dry eye treatment plan."

Dr. Starr also has dry eyes and uses the drug himself with good effect. "I keep it in my medicine cabinet, right near my toothbrush, because that way I'm sure to use it," he laughs.

Unlike Dr. Pflugfelder, who recommends patients refrigerate Restasis to reduce any stinging sensation from instilling the drug, Dr. Starr has never found the need to refrigerate it himself because he feels the drop is comfortable upon instillation.



Dr. Starr's treatment plan

"I liked Restasis from the beginning and I have increased my prescribing of it over the years as I've gained more experience and witnessed its impressive results," says Dr. Starr. The definition of dry eye disease has changed as knowledge of the disease continues to grow, he notes. "The most recent definition of dry eye disease from the Dry Eye WorkShop (DEWS) report notes hyperosmolarity and inflammation as key pathophysiologic factors, which supports the use of anti-inflammatory medication such as Restasis."

Dr. Starr agrees that treating dry eye disease requires an overall treatment plan tailored to each patient because dry eye is a multi-factorial disease. "I start most patients with early moderate and higher disease severity on Restasis because those patients are more likely to have significant ocular surface inflammation," he says. "A short course of the topical steroid Lotemax (lotoprednol, Bausch + Lomb, Tampa) with Restasis can be used to jump start the reduction of inflammation and help ease the mild burning associated with the initiation of Restasis."

Treating hyperosmolarity

Dr. Starr prescribes Restasis for most patients with significant hyperosmolarity as diagnosed by the TearLab device (TearLab Corporation, San Diego). Other elements of his dry eye treatment regimen can include AzaSite, which he finds helpful in treating anterior and posterior blepharitis off-label, omega-3 fatty acid supplementation, an emphasis on lid hygiene, warm compresses and lid massage, adjunctive use of artificial tears for symptom control and punctal plugs, among other treatments.

"We consider a decrease in the use of artificial tears a metric of success in treating this disease," Dr. Starr says. "A significant reduction in artificial tear use was seen in the pivotal clinical trials for Restasis."

Dr. Starr finds that educating patients in the proper use of Restasis is one of the primary keys to success with the drug. "First, patients must understand that Restasis is not an artificial tear and should not be used 'as needed,'" he says. "They should use one drop in the morning and one drop in the evening, no more and no less. They should expect some mild burning or stinging at first but a short-course of topical steroid and time will lessen this."

Dr. Starr says that some patients need as much as three to six months to obtain the full benefits of Restasis. This needs to be explained up front to maintain patient compliance through this initial period.

Dr. Yeu's treatment plan

Elizabeth Yeu, MD, of Virginia Eye Consultants in Norfolk, is another cornea specialist who both prescribes Restasis and uses it for her own dry eye condition. "I truly believe in the product for early-to-moderate dry eye," she says. "It does not work that well in the more severe case, stages three and four."

Dr. Yeu postpones using Restasis in patients who already have a burning sensation in their eyes. "First, we want to calm the eye down with a topical steroid before starting Restasis," she says. "If they have a foreign-body sensation or blurred vision but no burning we can start Restasis right away."

"Dr. Yeu says she postpones using Restasis in patients who already have a burning sensation in their eyes"

Episcleritis and lid inflammation

Dr. Yeu also likes to use Restasis for episcleritis, characterized by redness and inflammation. "With dry eye, you must customize the treatment for each patient," she says. "Younger patients tend to have more symptoms and few signs. For them, Restasis can be very helpful along with omega-3s. Older patients can be just the opposite, with strong signs and few symptoms. They don't seem to have the discomfort we see in younger patients. That could be because they have been on a number of medications and their senses have become a bit dulled over the years. But they do very well with Restasis, especially if they have a good tear film."

Dr. Yeu also treats inflamed lids as she wants to stop lid inflammation from spilling over onto and affecting the ocular surface. "I find that about 80% of my dry eye patients do very well on Restasis and just about all patients get some level of relief," she observes. "Patients who come off Restasis, for whatever reason, almost always get worse. Though they may not have seen improvement from the Restasis when they were using it, it was at least keeping the disease from getting worse. Restasis itself can only do so much, especially with patients who are dealing with other health factors that limit the effectiveness of the Restasis." **OM**

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Dry Eye Drug Development: When Will the Floodgates Open?

New therapies have the potential to turn the prescription market from a trickle to a deluge.

By René Luthe, Senior Associate Editor

Clinicians waiting for a new prescription drug for their long-suffering dry eye patients are going to have to wait a little longer. While many drug makers are on the case, their offerings will not be an option in the near future. Allergan's Restasis remains the only game in town in the way of prescription remedies. "The regulatory approval process for dry eye drugs is a nightmare," concedes EyeGate Pharma's president and chief executive officer, Stephen From.

What gives? Miami's William B. Trattler, MD, allows that part of the problem may be the FDA setting the bar too high. Yet the main problem, he believes, is dry eye's own peculiar nature. "Dry eye can be caused by aqueous deficiency or it can be due to poor tear film quality related to Meibomian gland dysfunction," Dr. Trattler notes. "Or, it can be a combination of these two forms of dry eye. Importantly, inflammation is present in both conditions."

However, not all the news is discouraging: Some drugs are inching closer to approval and researchers continue to gain valuable insights into the disease. Here's a snapshot of prescription dry eye remedies on the horizon.

More Obstacles Than Most

The combination of factors at work in dry eye disease is widely held to be the main reason for the lack of progress on the new-drug front. "The disease itself is highly variable," says Simon Chandler, PhD, director of clinical research at Ista Pharmaceuticals.

Eddy Anglade, MD, chief medical officer at Lux Biosciences, agrees. "There isn't a very good correlation between signs and symptoms," he says, "so trying to find that group of patients who have disease that will respond in a way that is convincing from a regulatory standpoint is challenging, given that the current regulatory approval standard is to demonstrate significance in a sign and in a symptom."

It has been so difficult to achieve, Mr. From points out, that no company has succeeded in getting a New Drug Application (NDA) filing approved. Where many drugs run aground, he says, is in trying to transition from phase 2 clinical trials to phase 3. "Most people worry about translating from animal models into humans," Mr. From explains. "In dry eye, we worry about phase 2 data translating into phase 3 — can somebody repeat a study a second time?"

Other experts familiar with FDA clinical trials and dry eye disease concur. Dry eye's variability means that when it is time for sponsors to scale their phase 2 trials to phase 3, the drug's efficacy may be harder to demonstrate. The disease's multifactorial nature also contributes to the difficulty in navigating the approval process. For each different cause, there is at least one way to potentially treat it. Matching the drug to the right kind of patient is crucial (see "Clinical Trial Pearls," below).