

The Once and Future Treatment of Dry Eye

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Up to 10 million Americans suffer the daily misery of chronic dry eye syndrome. Unrelenting ocular irritation and photophobia are a way of life. Dry eye syndrome, whether stemming from aqueous deficiency or accelerated tear evaporation, is the most common treatable eye condition you encounter in the clinic. In the face of such a stubborn and implacable malady, savvy clinicians use every conceivable countermeasure to bring some relief to their patients. Current treatments are essentially palliative. New therapies target the root causes of the disease.

Causes and Defects

The first step in managing dry eye is to determine what's causing it. Inflammation of the lacrimal gland and denervation of the cornea can curb tear production. Meibomian gland dysfunction and incomplete lid closure are frequently to

You have a broad range of therapies to alleviate the symptoms of dry eye. Researchers and drug manufacturers hope to expand your therapeutic arsenal.

blame for rapid tear evaporation. Obtain a history for systemic health factors, medications, environmental factors and anything else that may trigger or worsen symptoms.

"I see a lot of patients in this area who are taking a variety of over-the-counter medications for allergies or sinus problems, and those typically are antihistamines and decongestants," says James L. Fanelli, O.D., of Wilmington, N.C. "These people will get a pharmacologically induced dry eye because of all the medications."

Encourage patients to avoid environments that may exacerbate their discomfort, say a smoky barroom or a dusty attic. Maybe they can change their environment. "One thing that helps for people with really severe dry eye is to have them use a humidifier in their bedroom at night and moisten the air," Atlanta clinician Paul C. Ajamian, O.D., says.

Do a careful check of the lids. Meibomian gland stenosis and blepharitis are common triggers of dry eye. "Look at the lid margins for signs of

chronic staph lid disease," Dr. Ajamian advises. "A lot of dry eye patients have chronic staph, and yet we just focus on the dry eye portion and ignore the lid-hygiene portion."

Many patients who have had LASIK experience dry eye. Dry eye researcher Jeffrey P. Gilbard, M.D., attributes this to corneal denervation. "When you cut the flap, you cut the corneal nerves," he says. "And just as irritated eyes tear more, eyes that are numb tear less." A recent study in Australia found that 100% of LASIK patients receiving TheraTears—the artificial tears developed by Dr. Gilbard—were symptom-free at one month post-op compared to just 20% of the untreated control group. New York surgeon Eric D. Donnenfeld, M.D., is now investigating the efficacy of cyclosporine (Restasis, Allergan Pharmaceuticals) in treating post-LASIK dry eye.

What's Happening Now

Dry eye therapy is a sequence of palliative measures tailored to the severity of the presentation. Clinicians typically begin with non-pre-

Low-Viscosity Artificial Tears

GenTeal (CIBA Vision)
Hypotears PF (CIBA Vision)
Moisture Eyes (Bausch & Lomb Pharmaceuticals)
Refresh Plus (Allergan)
Refresh Tears (Allergan)
Tears Naturale Free (Alcon)
TheraTears (Advanced Vision Research)

Moderate-Viscosity Artificial Tears

Bion Tears (Alcon)
OcuCoat PF (B&L Pharmaceuticals)

High-Viscosity Artificial Tears

AquaSite (CIBA Vision)
Celluvisc (Allergan)
Murocel (B&L Pharmaceuticals)

served low-viscosity artificial tears prescribed every two hours or so. Among the more popular choices are GenTeal (CIBA Vision), Hypotears PF (CIBA Vision), Moisture Eyes (Bausch & Lomb Pharmaceuticals), Refresh Plus (Allergan), Refresh Tears (Allergan), Tears Naturale Free (Alcon) and TheraTears (Advanced Vision Research). Patients may especially like the convenience of GenTeal and Refresh Tears, which come bottled in a multi-dose formulation with a relatively non-toxic preservative that's neutralized upon instillation. Look for a multi-dose formulation of TheraTears come spring.

"TheraTears seems to be winning more and more support," Dr. Fanelli says. Rabbit studies showed that its electrolyte solution lowers elevated tear osmolarity and improves the eye's electrolyte balance. Even so, while Dr. Fanelli favors GenTeal and Refresh Plus, he says it usually comes down to trial-and-error. "There's no magic involved," he says. "It's a matter of finding the drop that gives you the longest-lasting and most-comfortable relief." Seattle clinician Kathy Yang Williams, O.D., favors preservative- and lanolin-free Hypotears PF for those with associated atopic eye disease to reduce the potential for a hypersensitivity reaction.

For more severe or refractory presentations, you may wish to graduate to moderate-viscosity artificial tears such as Bion Tears

(Alcon) or OcuCoat PF (B&L Pharmaceuticals), or high-viscosity products such as AquaSite (CIBA Vision), Celluvisc (Allergan) or Murocel (B&L Pharmaceuticals). As an alternative, these patients may find relief with the newer gel formulations GenTeal Gel (CIBA Vision) or Tears Again (OcuSoft). Ointments may work well for the most severe cases that require nighttime therapy.

Punctal plugs can be effective for moderate to severe dry eye when artificial tears alone don't bring relief. Some clinicians favor the CIBA Vision line of punctal plugs that come with a preloaded device that makes insertion easy. But don't wait too long to plug. "I don't think twice anymore about plugging," Dr. Fanelli says. "I'm not going to put

them through this regimen where they have to use tears every hour and ointments at night." He likes to do a monocular trial by plugging the upper and lower puncta of one eye for a few days to see if it works.

Especially severe and recalcitrant keratoconjunctivitis sicca may call for a short-term course of topical steroids. A 1999 study published in *Ophthalmology* by Peter Marsh, M.D., and Stephen Pflugfelder, M.D., found that a 2-week course of topical methylprednisolone relieved the irritation of dry eye, and in many patients that relief lasted weeks or months after they stopped therapy. Loteprednol etabonate 0.2% (Alrex, B&L Pharmaceuticals) or loteprednol etabonate 0.5% (Lotemax, B&L Pharmaceuticals) may be well-suited for this purpose

What Ever Happened to Restasis?

The people at Allergan Pharmaceuticals thought they had a good thing going when they approached the FDA last July for approval to market cyclosporine 0.05% (Restasis) as a treatment for dry eye. The two arms of the phase III clinical studies had gone well, demonstrating that the T-lymphocyte inhibitor effectively reduces the signs and symptoms of keratoconjunctivitis sicca with minimal adverse events.

But then something funny happened. The ophthalmic advisory panel for the FDA was less than impressed with Allergan's clinical data. The panelists issued a so-called "approvable letter" listing several points they wanted the company to address before they would recommend approval. "We have been reviewing the data and looking to see if in fact we could present the data from those studies in a way that would better present our case," Allergan spokesman Ira Haskell says.

"Unfortunately, the two arms of the phase III trial did not completely replicate themselves in terms of the signs and symptoms that reached statistical significance," investigator Steven E. Wilson, M.D., wrote in a paper presented last September at a Research to Prevent Blindness seminar. One problem was that cyclosporine's vehicle, a castor oil emulsion, may have worked a little too well in the trials.

"I don't know that the panel was that impressed that there was that much difference between the drug and the vehicle," says investigator Stephen Pflugfelder, M.D., who testified before the FDA panel on behalf of Allergan. "The vehicle itself is better than any artificial tear. You know, if they had compared the drug to artificial tears, they would have won hands down, I'm sure."

Allergan expects to hear back from the FDA by June, Mr. Haskell says. In the meantime, someone should consider packaging castor oil as a treatment for dry eye. Apparently, it's the next best thing to cyclosporine.—R.M.

because they're less likely than other steroids to increase intraocular pressure. "With the advent of some of the newer steroids, certainly it's nice to be able to prescribe medications like that without the risk of more serious complications," Dr. Williams says. Topical methylprednisolone 1% tid or qid for 3-4 weeks can be a safe and effective regimen.

You may need to address associated lid disease. In cases of staph blepharitis, Dr. Ajamian prescribes lid scrubs and a broad-spectrum antibiotic ointment such as polysporin. For dry eye symptoms due to meibomian gland disease, Terri Rose, O.D., of the Bascom Palmer Eye Institute in Miami, favors a 6-8 week course of oral doxycycline. "Dosing varies by physician, but an average course might be 100mg bid for 6-8 weeks," says Dr. Rose. "The use of an antibiotic in a non-infectious condition has to do with the effect of doxycycline on lipid production and its effectiveness as an anti-inflammatory agent."

What's to Come

The dry eye treatment that's attracted the most attention in the last year is one that hasn't even obtained FDA approval. Clinical investigators who have given their patients topical cyclosporine 0.05% (Restasis, Allergan Pharmaceuticals) say this immunomodulatory agent effectively reduces the signs and symptoms associated with keratoconjunctivitis sicca. Although Allergan was rebuffed in its bid last July to win FDA approval, the company has responded to the agency's concerns and hopes to get the green light to market the product by summertime.

Cyclosporine targets the immune-based inflammation that shuts down tear production in the lacrimal gland. "T-lymphocytes infiltrate the lacrimal gland, and

they cause inflammation," explains Dr. Donnenfeld, a clinical investigator for cyclosporine. "The acinar cells—those are the ones that secrete the tears—fibrose and die. The tear production stops, and you end up with a dry eye. What cyclosporine does, it's a specific T-cell modulator that inhibits T-lymphocytes reversibly, and in doing so stops the inflammatory cycle so that the inflammatory cells die a normal death and stop secreting the inflammatory mediators. The lacrimal gland tissue that's still viable comes

Gel Formulations

Gentel Gel (CIBA Vision)
Tears Again (OcuSoft)

Lubricating Ointments

Hypotears (CIBA Vision)
Moisture Eyes (B&L Pharmaceuticals)
Refresh PM (Allergan)
Duratears Naturale (Alcon)

back so that the patient starts inducing their own tears."

Although the FDA-mandated phase III trials showed that cyclosporine was clinically effective with negligible side effects (transient burning), Dr. Donnenfeld and other clinicians say it doesn't work for all patients. "One of the problems with cyclosporine is that we don't know who is going to be a good candidate for its use and who is not, and that's one of the things we're still working out right now," he says.

Further back in the pipeline is another potentially fruitful dry eye therapy, this one based on the sex-hormones known as androgens. Animal models show that androgens play a key role in regulating the function of both the lacrimal and meibomian glands. David A. Sullivan, Ph.D., of the Schepens Eye Research Institute in Boston recently found that women who lack

functioning androgen receptors had a significant increase in dry eye signs and symptoms. Another study revealed that patients with Sjögren's syndrome were androgen-deficient. Both studies support Dr. Sullivan's hypothesis that androgen-replacement therapy may benefit patients with lacrimal and meibomian gland dysfunction.

Allergan holds the license to any potential therapy based on Dr. Sullivan's research. The company put on hold a multicenter phase II study originally planned for last summer.

Still, Dr. Sullivan remains optimistic. "We think it looks promising," he says. "Every study we've been able to throw at it, with every control we can, so far they've been consistent with the hypothesis."

Keep an eye on what's happening at Bascom Palmer. Searching for a target at which to aim a potential therapy, Dr. Pflugfelder has been looking for molecules that are elevated in dry eye but normal in healthy individuals. He thinks he's found a collagenase enzyme that fits the bill. "There's one specifically called MMP9 that's very high in dry eye patients in their tear fluid and almost nondetectable in normals," he says. "For the first time, I have a marker that goes up in dry eye and not in normal eyes. I think it's definitely something to look into, inhibiting that." Interestingly, we already have a medication that acts as a potent inhibitor of MMP9—the tetracyclines. Dr. Pflugfelder hopes to develop other therapies based on what he's learning.

Dry eye will remain fertile ground for research as long as patients continue to suffer. Chronic keratoconjunctivitis sicca is a miserable way to go through life. Just ask your patients. They'll appreciate anything you can do to ameliorate their lot. ♦