REVIEW of Ophthalmology

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PUBLISHED 15 FEBRUARY 2003

New Thinking Spurs New Products

With the market for dry-eye products already huge and growing, the need for effective therapy is leading to novel approaches that move beyond tear replacement. This article reviews some of those efforts that have come to fruition in recent product introductions.

Restasis, at Last

The late-December Food and Drug Administration approval of Allergan's Restasis (cyclosporine ophthalmic emulsion 0.5%) ended years of development, testing and regulatory hurdles for the company. The drug is the first therapeutic dry eye product approved and may have paved the way for other competitors.

The product is a reflection of an evolving understanding of the dry-eye disease process. Restasis was designed for patients with inadequate tear production due to ocular inflammation associated with keratoconjunctivitis sicca. The inflammatory pathophysiology until recent years was thought to be limited to a small subset of dry-eye conditions.

Regulatory fits and starts marked the history of Allergan's cyclosporin product, finally approved in December 2002.

Peter McDonnell, MD, of the University of California, Irvine, who participated in the Restasis clinical trials, explains, "It's been known for some time that that diseases like rheumatoid arthritis and Sjögrens are autoimmune conditions in which lymphocytes essentially the attack the patient's own lacrimal gland, and there is destruction of tissue and dysfunction of the gland. It was thought that this was very much the exception, just one small subset of dry-eye patients. The data that has been generated over the last five to 10 years show is that this is not really a great exception, that, in fact, a very common phenomenon in a great number of patients with dry eye is an underlying local disorder of immunity or inflammation that causes this same type of lacrimal dysfunction."

Michael Lemp, MD, a clinical professor of ophthalmology at Georgetown University School of Medicine, says the action of cyclosporin-A downregulates the inflammatory response and allows those cells to recover their normal activity. "By modulating the immune response, which sets up inflammation, [cyclosporin-A] controls the inflammatory response," says Dr.

glands of the eyelid, leads to a dysfunction of acinar cells, the secreting cells in the lacrimal glands that produce the aqueous portion of the tears. Those cells become dysfunctional and do not produce tears either of normal quantity or quality."

Allergan calls the product a "partial immunomodulator," though its exact mechanism of action is not known.

The Restasis Phase III submission was based on four multicenter, randomized, controlled trials of 1,200 patients diagnosed as suffering from moderate to severe keratoconjunctivitis sicca. The most common side effects in the trials were ocular burning (approximately 17 percent of patients), and conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging and blurring (1 to 5 percent).

It may take up to six months for the product to take full effect, though Dr. Lemp points out that this is "not unreasonable when you understand how it works. This is a disease process that takes a long time for an inflammation to develop and for the cells to become dysfunctional. And to restore the environment in which the cells can recover is going to take some time too."

Dave Power, Allergan's director of Global Pharmaceutical Marketing, points out that the emulsion vehicle in which the cyclosporin is dissolved provides some comfort benefits fairly quickly. "Certainly in our studies we saw improvements in patient comfort at the first month and that continued to get better as the disease heals," he says. "We need to educate the doctors on how this drug works and why it takes some time for it to have its full effect. That's not a hard sell for the doctor to tell a patient who has been coming to his office for several years and not gotten the kind of relief that he's looking for to stick with this product, because there's really nothing else out there for him."

With the addition of Endura, intended for moderate to severe cases, the Refresh line extends to all levels of dry eye.

Dr. McDonnell agrees. "I've felt for some time fairly impotent in helping these patients with severe dry eye, whose lives are really disordered by this condition," he says. "Now to have something where we can finally address the underlying condition is pretty exciting."

A New Landscape

Dr. Lemp believes the willingness of the FDA to reconsider data based on the changing understanding of dry eye bodes well not just for patients and physicians, but for industry as well.

"The data from the first two Phase III clinical trials has been available for several years and

new trials that supported the drug's FDA submission, this approval "involved the agency's willingness to relook at data and reinterpret it in terms of defining efficacy," he says. "There has been a gradual increasing awareness that [dry eye] is a difficult nut to crack, a gradual recognition that has been coming on for years. So this is absolutely a positive development for the agency and entirely appropriate."

That willingness to reconsider dry-eye data may benefit Durham, N.C.'s Inspire Pharmaceuticals, which is preparing to seek approval on its own product, diquafosol tetrasodium (INS365 Ophthalmic). One Phase II trial and two Phase III trials have been conducted, and a Phase IIIb trial is ongoing.
Inspire announced in October 2002 that the NDA filing would be based on safety and efficacy data from the completed Phase II and Phase III trials. As well as safety and tolerability, the trials of INS365 have demonstrated statistically significant improvement compared to placebo in corneal and conjunctival staining.

The content and format of a New Drug Application for the product submission were agreed to with the FDA in a pre-NDA meeting held in January 2003.
"We believe this overall clinical package is strong, and we now have clarity on FDA requirements for the content and format of the NDA submission," said Christy L. Shaffer, PhD, CEO of Inspire. "Our top priority is to prepare and submit a high-quality NDA mid-year."

New in OTC

Another new product introduced last year extended the Refresh (Allergan) line of tear supplements. Refresh Endura. Unlike the other preserved products in the Refresh line, Endura is unpreserved and features an emulsion formula that keeps the product active on the eye longer, says the company.

Erika Carlucci, product manager for the Refresh line, says, "Endura is intended for the moderate to severe dry-eye patient, the ones who tend to go their eye doctor." She calls the product "a new type of technology that the over-the-counter market hasn't seen."

Peter Simmons, PhD, senior scientist at Allergan R&D, explains, "The big difference is this oil-based emulsion and the structure of the emulsion is such that it's in a low electrolyte formula in the container, then when it hits the eye and interacts with the tears, the electrolytes in the tears cause the emulsion to break down, and that releases the oil. So the oil can then migrate and supplement the lipid layer in the tears."

Castor oil has been shown to be effective in treating patients with meibomian gland dysfunction. A randomized, placebo-controlled Japanese study used a low-concentration

noninflamed MGD whose symptoms had not improved with conventional artificial tears, antibiotics, and corticosteroids.1 Nine patients demonstrated aqueous tear deficiency of Schirmer testing, with four of these diagnosed with Sjögren's. Excluded were patients with anterior blepharitis of more than moderate severity, infectious conjunctivitis, acute MGD, and excessive expression of meibum. For two separate two-week periods, subjects were randomly assigned to receive oil eye drops or placebo six times daily.

Pre- and post-study examination included tear evaporation assessment, rose bengal and fluorescein staining, tear breakup time and a subjective patient assessment of comfort. Symptom scores, as well as each of the objective measures, showed significant improvement in the treatment period vs. the placebo period. The authors postulate several mechanisms for the improvement in the tear stability including lipid spreading over the ocular surface, greater ease of meibum expression, prevention of tear evaporation and the lubricating effect of the oil.

Patients may notice an unusual sensation when they first encounter Endura. "When that emulsion breaks down, within a minute or so, some people get a sensation, a very transient bit of a sting, or they just notice that something is there," says Dr. Simmons. "It behaves differently from most eye drops that are usually very soothing initially and wear off rapidly as the fluid tends to drain from the eye. The oil component, we think, will reside on the lower lid, float on the tear fluid and stay around a lot longer."

Roanoke, Va., ophthalmologist John Sheppard says he's found the solution especially effective for patients with lipid-deficiency dry eye, such as those with blepharitis. "It comes in a single-dose unit, so it's preservative free, which is great. Because it's an SDU, it's not as cost-effective and a little more inconvenient to use, but in many cases, it's well worth those minor adaptations."

He's also adding it with good success to antibiotic therapy for certain patients with meibomian disease or rosacea. For the majority of patients who tolerate the doxycyclene he normally prescribes, the therapy can take a few months to be fully effective. In the interim, he says, Endura can provide symptomatic relief.

Advanced Vision Research has added two products to its TheraTears line.

The Nutritional Route

Another approach to improving tear film composition, this one through nutritional means, is TheraTears Nutrition, one of two new products from Advanced Vision Research, of Woburn,

In the body, omega-3s are acted on to produce prostaglandin E3 and leukotriene B5. These two eicosanoids decrease inflammation. Omega 3s also decrease gene expression of proinflammatory interleukins, tumor necrosis factor-alpha and cylooxygenase, as well as decreasing the activity of proteoglycan-degrading enzymes.

In addition, the meibomian glands use essential fatty acids in the production of the lipid component of the tear film, says Jeffrey Gilbard, MD, founder of Advanced Vision Research. He cites studies showing the polar lipid profiles of meibomian gland secretions in female Sjögren's patients are controlled by the dietary intake of omega-3 essential fatty acids, as well as clinical reports of clearer and thinner oils with omega-3 treatment. EFAs also play a role in inhibiting production of arachidonic acid and promoting the production of prostaglandin E1, which has been shown to stimulate aqueous tear production.

The company has also introduced TheraTears Liquid Gel, a preservative-free, hypotonic electrolyte-balanced liquid gel for dry eye. The gel, for nighttime or daytime use, is designed to avoid lid crusting and blurred vision, according to the company.

1. Goto E, Shimazaki J, Monden, Y, et al. Low-concentration Homogenized Castor Oil Eye Drops for Noninflamed ObstructiveMeibomian Gland Dysfunction. Ophthalmology 109:11;2030-2035.