Increased tear production: Restasis approval a milestone for dry eye

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By Lynda Charters

The FDA approval of cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan) Dec. 26 marked a landmark for ophthalmology. The eye drop therapy for moderate to severe keratoconjunctivitis sicca is unique in that it treats the inflammatory process that causes the condition, and not just its symptoms. Allergan estimates that the product will be commercially available this spring.

The three-arm study of cyclosporine for the treatment of dry eye began about 5 years ago and included two concentrations of cyclosporine (0.1% and 0.05%) that were compared with a novel lipid emulsion vehicle (placebo). Moderate to severe dry eye was defined as the presence of corneal staining, Schirmer scores less than 5 mm, and frank conjunctival and corneal staining.

Investigators were masked as to which eye drop the patients instilled twice daily for 6 months. The eyes were evaluated by global assessment of the severity of the dry eye at 1, 3, and 6 months after the onset of treatment. Schirmer tests, corneal and conjunctival staining, and tear breakup time tests were repeated at each follow-up visit.

The frequency of the use of adjunctive artificial tears to relieve dry eye symptoms was also recorded as a measure of the efficacy of cyclosporine. A small subgroup of patients underwent biopsy of the conjunctiva before and after 6 months of treatment to detect inflammatory cells; the results with the two concentrations of cyclosporine were then compared with the controls.

Therapy significance Cyclosporine is eagerly awaited by members of the ophthalmic community who treat patients with chronic dry eye resulting from ocular inflammation, because it is the only therapy that increases tear production and tear quality, according to Eric D. Donnenfeld, MD, a principal investigator in the multicenter Restasis study.

Dr. Donnenfeld

"In the more than 800 patients who participated in the Restasis study, a statistically significant number of patients who received cyclosporine had more tear production documented by increased Schirmer scores, decreased corneal and conjunctival staining, and more importantly, there was a global improvement in the patients' assessment of their dry eye symptoms compared with the controls," said Dr. Donnenfeld emphasized. He is also a founding partner of Ophthalmic Consultants of Long Island, Rockville Centre, NY, and associate professor of ophthalmology, New York University Medical Center, New York.

Dr. McDonnell

"From a pathologic perspective, the most exciting finding was that when the conjunctival biopsies were performed there was a significant increase in the numbers of goblet cells, indicating that the patients who received cyclosporine made more goblet cells and produced more mucin, and there was a decrease in the inflammatory markers in the conjunctiva, indicating that there was less inflammation there," he added.

"Restasis allows patients to make their own physiologically normal tears," he said. "The availability of this drug is a landmark event that is equivalent to the advent of phacoemulsification or antiviral therapy."

Peter J. McDonnell, MD, professor and chair, department of ophthalmology, University of California, Irvine, and colleagues Roy Chuck, MD, PhD, and Ramin Pirnazar, MD, principal investigator, tested cyclo-sporine according to the same or similar protocols in about 100 patients at the University of California, and a control group of patients received the placebo formulation.

"One measure of efficacy of Restasis was the less frequent use of adjunctive tears, which was certainly apparent in many of our patients," Dr. McDonnell said. "Other measures of efficacy were that a high percentage of our patients generally believed that their condition had improved and at the end of the study wanted to continue receiving cyclosporine.

"In addition, our patients typically had less corneal staining, and in some patients the Schirmer test scores actually increased substantially," he said. "Unfortunately, there is no single test that is considered the single standard for patients with dry eye and the results can vary."

Dr. McDonnell noted that 75% to 80% of patients who received cyclosporine had improvement.

The drug appears to be very safe; 17% of patients reported transient ocular burning after instillation of the drops, and from 1% to 5% reported conjunctival hyperemia, discharge, epiphora, eye pain, foreign-body sensation, pruritus, stinging, and visual disturbance (mostly blurring). Cyclosporine is not known to cause cataract or infections, and it does not inhibit wound healing.

Dr. McDonnell pointed out that despite that fact that many patients reported stinging and burning upon instillation, none of his patients left the study for this reason, because the positive effect of the drug was substantial. He also noted that the drug is contraindicated in patients with herpetic disease because of the drug's possible effect on lymphocytes. Herpetic disease was an exclusion criterion for these trials.

The mechanism by which cyclosporine improves tear production is unclear. In dry eye the lymphocytes that normally pass through the lacrimal gland instead aggregate in the gland and cause inflammation. Cyclosporine reverses the inflammatory process and allows lymphocytes to pass through the lacrimal gland and not cause damage, Dr. Donnenfeld explained.

An interesting result of this study, but one whose ultimate outcome is presently unknown, is that cyclosporine may cure dry eye in some patients rather than having to be used chronically.

"Although the trial did not allow this type of experimentation, after patients completed the study some reported that their condition stabilized without cyclosporine," Dr. McDonnell said. "I think this result may depend on the point in the disease at which we begin to treat. If it is possible to eliminate the inflammation completely, my hope is that some patients will experience a 'cure.' I hope we will be able to eliminate the need for treatment or be able to taper the treatment so that they no longer have to use the drug twice a day.

"I believe that historically we have waited far too long to diagnose dry eye disease and treat our patients," he added. "We are now treating patients who are perhaps considered to have 'mild' or 'moderate' dry eye, but who have been suffering for a long time and the inflammation and dryness have been allowed to progress. We should consider intervening much earlier in the process, instead of waiting for postmenopausal women, especially, to develop severe debilitating disease, with significant limitation of quality of life. Perhaps we should be testing tear production when patients reach age 30 to detect early manifestations of dry eye disease, when we have a window of opportunity to prevent progression."

Dr. Donnenfeld echoed that sentiment.

"I believe that the patients who are the best candidates for treatment with cyclosporine have not yet been identified," Dr. Donnenfeld said "Patients should be treated with cyclosporine at the onset of the development of dry eye. In the early acute inflammatory process, Restasis can reverse the process and allow the patient to produce his or her own tears. We do not want to postpone treatment until the lacrimal gland becomes fibrotic and not sustainable."

Dr. McDonnell also pointed out that the efficacy of cyclosporine was not assessed in patients with punctal plugs.

"Intuitively, Restasis should be effective in these patients, but it has not specifically been established to be safe and effective in these patients," Dr. McDonnell said. "The dosing may have to be adjusted and there is a question about whether the drop would last as long in the tear film. Perhaps the dose could be decreased to once daily in some patients, but those with especially severe disease might have to be treated aggressively, with twice-daily dosing. More patients need to be tested to answer these questions."

Dr. McDonnell is eager to begin treating his patients with dry eye who did not meet the inclusion criteria.

"Dry eye is one of the most common and debilitating diseases that ophthalmologists see in clinical practice," Dr. Donnenfeld said. "Tens of millions of patients in the United States have dry eye.

"For the first time, we can offer these patients a drug that might reverse their dry eye and help resolve the disease," he concluded. "The advent of this drug acknowledges for the first time that dry eye is an inflammatory disease that should be treated with immunomodulation and not just tear supplementation."

Marketing approach Regarding marketing, David Power, director of global pharmaceutical marketing, Allergan, explained that the drug will be marketed to physicians in March and April, but not directly to consumers. Public relations initiatives are being planned to raise awareness of dry eye disease in the general public and the availability of cyclosporine so that individuals with symptoms can seek help from ophthalmologists. He said Allergan will be working closely with patient support groups.

"Allergan is very excited about the FDA approval of Restasis," said Lester J. Kaplan, PhD, president/research and development, Allergan. "This is a culmination of Allergan's research and development team's pioneering work in the field of ocular surface disease. Allergan . . . is pleased about the ability to address this unmet need of both patients and ophthalmologists by offering the first therapeutic option for the treatment of chronic dry eye disease."