MORE OPTIONS IN DRY EYE THERAPEUTICS

As additional treatments become available, the role of diagnosis is elevated.

BY KARL G. STONECIPHER, MD

Diagnosis, *treatment*, and *options* are three of the most gratifying words that can be said to a patient who presents with an amorphous and recalcitrant ocular problem. For more years than we eye care providers would like to admit, patients who presented with signs and/or symptoms of dry eye disease (DED) could not get a distinct diagnosis and were treated with a random array of artificial tears, and other options were nonexistent.

Fortunately, the situation has changed. Effective therapeutic options for the treatment of DED such as Restasis (cyclosporine ophthalmic emulsion 0.05%; Allergan) are available, and others are in the pipeline. The frequency with which patients present with symptoms of DED as well as the need for an optimal ocular surface, such as prior to LASIK and premium IOL surgery, continues to grow in my practice and others'. Digital eye strain from the pervasive use of smartphones, the high rates of diabetes—which are associated with an increased rate of DED—and environmental issues such as air pollution are among the causes linked to the rise in DED.

GREAT STRIDES

DED represents a widespread and growing problem for the daily visual function of more than 30 million Americans, and it affects the outcomes of lenticular and laser vision surgery in thousands more. Recognition of DED as far more than a nuisance lit a fire under stakeholders in the ophthalmic community.[1] Consequently, the past decade has brought great strides with respect to DED awareness, diagnosis, and treatment. The International Task Force guidelines proposed a classification of DED severity based on clinical signs and symptoms (levels 1-4) and developed treatment algorithms and recommendations based on symptoms such as discomfort, visual disturbances, corneal and conjunctival staining, meibomian gland dysfunction, tear breakup time, and Schirmer scores.[2]

DIAGNOSTIC MODALITIES

Since the guidelines were released, progress has come in the form of numerous diagnostic modalities designed to identify the type of DED afflicting patients. As the landscape of treatment options evolves, the importance of careful diagnosis is elevated. Once, we treated patients with whatever therapy was available regardless of the specific nature of their symptoms, because our options were limited. Now, we can identify specific nuances, and in the not-too-distant future, we will be able to offer targeted treatment. An expanding array of diagnostic tools plays a role in documenting the prevalence and type of DED (eg, lacrimal gland disease, mixed mechanism disease, meibomian gland dysfunction, and aqueous tear deficiency). Modalities such as tear osmolarity (TearLab), matrix metallopeptidase 9 detection (InflammaDry; Rapid Pathogen Screening), and LipiView and LipiView II (TearScience) with meibomian gland imaging and testing for Sjögren disease via early disease stage antibody detection (Sjö; Bausch + Lomb) are among the approaches available to help us plan our targeted treatment approaches.

Progress in the area of therapeutics is also being made, first with the approval and availability of cyclosporine and, now, with substantial research and development of numerous other options currently in the pipeline. Until cyclosporine became available, our options were mostly limited to short-term pulsed topical steroid therapy such as Lotemax (loteprednol 0.5% gel; Bausch + Lomb); advanced artificial tear formulations such as Refresh Optive Advanced (Allergan), Systane Balance (Alcon), and Soothe XP (Bausch + Lomb); and punctal plugs and autologous serum drops. Cyclosporine, which is a mainstay in my practice, is approved for patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (levels 3 and 4). We very well may need to diagnose this disease earlier; when cyclosporine is used sooner (levels 1 and 2), my patients seem to do better.

CHANGE ON THE HORIZON

In October 2015, Shire announced positive topline results from OPUS-3, a phase 3 efficacy and safety study of lifitegrast versus placebo. OPUS-3 met the primary

MORE THAN ENOUGH TO GO AROUND

Pharma executive says the outlook for the dry eye disease market is bright.

BY STEPHEN DAILY, EXECUTIVE EDITOR, NEWS, BMC

In a conference call with investors to discuss third-quarter earnings in November 2015, Allergan executives were asked during the Q&A portion of the call what their outlook is for Restasis (cyclosporine ophthalmic emulsion 0.05%), given the recent positive data for Shire Pharmaceuticals' dry eye disease (DED) drug candidate lifitegrast, which if approved would serve as the first pharmacological competitor for cyclosporine.

"I don't believe this is going to be a fight to the death between Shire and Allergan," said Bill Meury, president, branded pharma, at Allergan. "I said before that the gap between the prevalent [DED] population and the prescription-treated population is enormous. It's larger than it is in most categories. The importance of [DED] is clear, and it's getting more and more attention because of the impact it has on quality of life, the impact that it could have on vision, and positive postop[erative] outcomes."

Shire recently announced topline results from OPUS-3, a phase 3 efficacy and safety study of lifitegrast. In the trial, the drug met the single primary endpoint for patient-reported symptoms of ocular dryness (mean change in eye dryness score from baseline to week 12 [$P = .0007$]) and the secondary endpoints of symptom improvement at days 14 and 42 ($P < .0001$ for both endpoints).

The OPUS-3 data came after the FDA formally declined lifitegrast in October 2015. At that time, the government agency requested further clinical tests along with more information about product quality. Shire says the OPUS-3 data put the drug candidate back on track for a commercial launch in 2016.

Mr. Meury stated that the DED market is large enough to support both drugs: "When you look at the data set between the drugs, I would simply say that we will have to see how lifitegrast holds up in the real world. … There's no doubt eye care professionals are going to try something new, but I believe, long term, this category has the potential to double, so there's more than enough to go around."

Research and consulting firm GlobalData concurs. In a report, GlobalData stated that the global treatment market for DED will more than double in value from about $2.2 billion in 2014 to an estimated $4.6 billion by 2024, representing a compound annual growth rate of 7.9%.[1]

The growth will be driven primarily by the introduction of novel drugs, most notably lifitegrast, the report stated.

Catherine Daly, PhD, GlobalData's senior analyst covering neurology and ophthalmology, stated in a news release that the paucity of DED treatments in the US and European markets will allow Shire to secure strong uptake and a sizable market share for lifitegrast.

"GlobalData expects that lifitegrast, which is anticipated to launch in the US in late 2016, will eventually reach peak sales of $1 billion across the nine (major markets) earning the drug blockbuster status," Ms. Daly said. "Furthermore, Allergan's blockbuster [DED] drug, Restasis, which generated an estimated $1.33 billion in US sales in 2014, is expected to launch in the European markets during the forecast period and will secure a sizable patient share."

Allergan is also investing in the potential of an additional DED therapy in late-stage development. The company has entered into an exclusive licensing agreement with Mimetogen Pharmaceuticals to develop and commercialize tavilermide (MIM-D3), a topical formulation of a novel small-molecule TrkA agonist for the treatment of DED.

Under the terms of the agreement, Allergan will make an upfront payment of $50 million to Mimetogen and will fund phase 3 development of tavilermide. Mimetogen will additionally be entitled to receive potential milestone payments and royalties based on commercialization of the product.

Tavilermide is a small cyclic peptidomimetic of nerve growth factor, a naturally occurring protein in the eye responsible for the maintenance of corneal nerves and epithelium. Tavilermide is differentiated from other investigational therapies in DED, because it induces the production of mucin, a naturally occurring component of the tear film, and works upstream prior to inflammation, according to Allergan. Tavilermide is currently being evaluated in two multicenter phase 3 clinical studies in the United States.

Ms. Daly of GlobalData said that Mimetogen's MIM-D3, Mitotech's Visomitin, and RegeneRx's RGN-259 are also expected to see strong sales growth by 2024, because these first-in-class drugs all have different therapeutic benefits to offer to DED patients.

In addition, Mr. Meury said during the conference call that Allergan is going to launch a multidose, preservative-free form of cyclosporine in the second half of 2016. The new formulation will be more convenient for patients, he added, because it will be easier to administer.

1. PharmaPoint: Dry Eye Syndrome – Global Drug Forecast and Market Assessment to 2024. www.globaldata.com. Accessed November 5, 2015.

> "If approved, lifitegrast will be the first new treatment for DED since cyclosporine."

endpoint of significantly improving patient-reported symptoms of DED from baseline to day 84 ($P = .0007$). Additionally, OPUS-3 met the secondary endpoints of symptom improvement from baseline to days 14 and 42 ($P < .0001$ for both endpoints). Shire plans to use these data as part of its resubmission of the company's new drug application for lifitegrast for the treatment of the signs and symptoms of DED in the first quarter of 2016.

If approved, lifitegrast will be the first new treatment for DED since cyclosporine. Some suggest that AzaSite (azithromycin ophthalmic solution; Akorn) holds that title. The drug is approved solely for bacterial conjunctivitis, however, whereas the new drug application for lifitegrast specifically requests an indication for the treatment of DED.

COMPARING THE TWO THERAPIES

Comparisons of cyclosporine and lifitegrast are inevitable, and speculation regarding whether the new entrant into the marketplace will unseat the market leader is in full swing. I do not foresee this happening. I believe that the availability of other options will draw attention to the market and spur overall growth. Given the vast market for DED therapies, there should be more than enough demand to support the market share needs of these two pharmaceuticals (see *More Than Enough to Go Around.*)

Also, lifitegrast and cyclosporine have different mechanisms of action and are appropriate in distinct instances based on different diagnostic algorithms. Lifitegrast mimics lymphocyte function antigen-1. This process prevents the activation of intercellular adhesion molecule-1, which is expressed on the inflamed epithelial cell surface. DED-associated inflammation is typically mediated by T cells that feature increased expression of intracellular adhesion molecule-1. Lifitegrast essentially breaks the cycle of T cell-mediated inflammatory response on the ocular surface.

Cyclosporine acts as a selective inhibitor of interleukin-2 release during the activation of T cells and causes cell-mediated immune response suppression.[3,4] Cyclosporine's mechanism of action is based on its effects on subconjunctival and lacrimal gland inflammation, resulting in an increase in tear production and conjunctival goblet cell density in a significant number of patients with moderate to severe DED who received treatment.[5,6]

Lifitegrast has a 7.0 pH, which is similar to that of the natural tear film. Based on studies reported to date, the drug is potentially complementary to cyclosporine therapy. This opens up the possibility of a belt-and-suspenders approach to patients who could benefit from the combination of an anti-inflammatory and an immunosuppressive mechanism of action. It has been widely reported that lifitegrast acts fast, and some see this as a potential benefit over cyclosporine, because the latter is often described as having a delayed onset of action. Many of my DED patients experience early relief with cyclosporine; its reputation for a delayed onset of action is a vestigial artifact of the clinical studies upon which its approval was based. Until lifitegrast has long-term follow-up in clinical practice, I believe it is far too soon to determine whether or not it acts quickly in any, some, or all patients.

CONCLUSION

The evolution of DED treatment has taken us from near helplessness to finally having a therapeutic option that offers relief to a significant proportion of patients. I am hopeful that the next drug to make its way into the DED armamentarium can move treatment along its evolutionary pathway. Meanwhile, I will continue to use cyclosporine as my first-line treatment and consider it the gold standard in patients who were once hard to treat until long-term, real-world evidence suggests that I should alter my algorithm. ■

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