Dry Eye Disease: a New Era Approaches

With numerous companies investing in research, a revolution in treatment is on the horizon.

BY CHRISTOPHER E. STARR, MD

The days of handing a bottle of artificial tears to a patient complaining of dry eyes and hoping not to see him or her again are gone. Today, we ophthalmologists recognize dry eye disease (DED) as real pathology that can be accurately diagnosed and effectively treated. Simply put, the report of the International Dry Eye WorkShop in 2007 revealed that inflammation is the key underlying pathophysiologic mechanism of DED and a part of its definition.[1] With that knowledge, there is great interest in targeting various parts of the inflammatory pathway in order to manage DED effectively. At present, only one pharmaceutical is FDA approved for the treatment of inflammation associated with chronic DED: cyclosporine ophthalmic emulsion 0.05% (Restasis; Allergan, Inc.). Because DED is one of the most common diagnoses we make, companies understand the immense value of the dry eye market, and as a result, drug development is booming.

CURRENT OPTIONS

Artificial tears have always played a role in DED therapy, primarily for the temporary relief of symptoms. For that reason, there is a wide array of these products with varying characteristics (thin, thick, lipid replacement, hypo-osmolarity, etc.). An argument could be made that, by decreasing the friction of the eyelids' passage over the corneal and conjunctival epithelium, simple lubrication of the ocular surface may lessen inflammation, albeit slightly. Topical cyclosporine has been our only FDA-approved, true antiinflammatory for DED and has appropriately become the mainstay of treating moderate and more severe DED.

Many of us prescribe short courses of topical corticosteroids—usually milder agents such as loteprednol (Lotemax; Bausch + Lomb)—when initiating therapy with cyclosporine. This adjunctive therapy helps to rapidly reduce ocular surface inflammation, but of course, topical corticosteroids cannot be used safely long term due to the risk of elevated IOP, the development of cataracts, and the potentiation of infection.

Any conversation about DED would be incomplete without a mention of evaporative dryness from meibomian gland dysfunction (MGD), which may be the most common cause of the disease. Although no topical pharmaceutical has been approved for the treatment of MGD or blepharitis, a short course of topical azithromycin (AzaSite; Merck & Co., Inc.) is often used off label in addition to more traditional treatments such as warm compresses, lid hygiene, lid massage, oral doxycycline, and increased intake of omega-3 fatty acids. A newer approved therapeutic device for MGD is the LipiFlow Thermal Pulsation System (TearScience, Inc.), a sophisticated heater and massager of the eyelids.

THE FUTURE: A BRIEF OVERVIEW OF THE PHARMACEUTICAL PIPELINE

Lifitegrast (SAR 1118; Shire, which recently bought SARcode Bioscience) is an integrin antagonist that is dosed twice daily for 12 weeks in studies. Patients are currently being recruited for a second phase 3 trial (OPUS-2), and a safety study is underway.[2,3] Lifitegrast blocks the interaction of lymphocyte-associated antigen-1 and intercellular adhesion molecule (LFA-1 and ICAM-1), thereby reducing T-cell activation, proliferation and migration as well as cytokine release on the ocular surface.

InSite Vision has been studying a combination of the nonsteroidal antiinflammatory drug bromfenac with the company's proprietary vehicle DuraSite. ISV-101 has completed a phase 1 study.[4]

RX-10045 (Resolvyx Pharmaceuticals in partnership with Celtic Therapeutics) is a topical synthetic resolvin analog. This drug has completed a phase 2 study for DED.[5]

MIM-D3 (Mimetogen Pharmaceuticals Inc.) is a small-molecule mimetic of nerve growth factor. As a secretagogue, it is designed to increase the production of mucin and tears. The phase 2 safety and efficacy study of this drug for the treatment of DED is complete.[6,7]

Rebamipide ophthalmic suspension (OPC-12759; Otsuka Pharmaceuticals) is approved in Japan and is the subject of

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phase 3 trials in the United States. This drug also increases the production of mucin.[8]

A phase 3 trial of CF101 (Can-Fite BioPharma Ltd.), an oral adenosine receptor agonist, for the treatment of DED is currently enrolling patients. They will be treated with the drug or placebo twice daily for 24 weeks.[9]

The FDA recently approved the Investigational New Drug Application for RU-101 (R-Tech Ueno), a recombinant human serum albinum-containing ophthalmic solution for the treatment of severe DED. According to a press release from the company on April 26, 2013, phase 1 and 2 clinical trials are being planned in the United States.

A recently published, small, 6-month trial of 3% diquafosol showed improved signs and symptoms in aqueous-deficient DED at 1 month.[10]

CONCLUSION

Who knows how long it will take, but this renaissance in DED research and innovation will increase our arsenal against this ubiquitous disease. Will we start with one medication, assess its efficacy, and then add to it, as we often do for glaucoma? Will we begin with multiple drops that have different but potentially synergistic mechanisms of action? Given a wider array of pharmaceuticals that target different pathways in DED pathogenesis combined with more sensitive and objective diagnostics, I anticipate a revitalized interest in DED among clinicians and an unprecedented era of successful treatment. ■

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1. Research in dry eye: report of the Research Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf.2007;5(2):179-193.
2. Safety study of lifitegrast to treat dry eye (SONATA). http://clinicaltrials.gov/ct2/show/NCT01636206?term=sarcode&rank=2. Updated February 27, 2013. Accessed June 11, 2013.
3. A phase 3 study to evaluate the efficacy of lifitegrast in subjects with dry eye. http://clinicaltrials.gov/ct2/show/NCT01743729?term=sarcode&rank=1. Updated June 7, 2013. Accessed June 11, 2013.
4. Product pipeline. InSite Vision website. http://www.insitevision.com/product_pipeline. Accessed June 11, 2013.
5. RX-10045. Resolvyx website. http://www.resolvyx.com/products/rx-10045.asp. Accessed June 13, 2013.
6. Mimetogen Pharmaceuticals Inc. announces positive top line data from phase 2 clinical trial of MIM-D3 for dry eye disease. Mimetogen Pharmaceuticals Inc. website. http://www.mimetogen.com. Published June 26, 2011. Accessed June 13, 2013.
7. Safety and efficacy study of MIM-D3 ophthalmic solution for the treatment of dry eye. http://clinicaltrials.gov/ct2/show/NCT01257607. Updated October 22, 2012. Accessed June 13, 2013.
8. Osterweil N. Dry eye symptoms eased by rebamipide, a mucin secretagogue, Medscape Medical News. April 4, 2013. http://www.medscape.com/viewarticle/781948. Accessed June 11, 2013.
9. Trial of CF101 to treat patients with dry eye disease. http://clinicaltrials.gov/ct2/show/NCT01235234. Updated May 8, 2013. Accessed June 13, 2013.
10. Koh S, Ikeda C, Takai Y, et al. Long-term results of treatment with diquafosol ophthalmic solution for aqueous-deficient dry eye [published online ahead of print June 6, 2013]. Jpn J Ophthalmol. doi:10.1007/s10384-013-0251-y.