Blepharitis is a common inflammatory disease of the eyelid that may be infectious in nature. The posterior form affects the posterior lamella of the eyelid and inflames the meibomian glands, whereas anterior blepharitis involves the anterior lamella of the eyelid and the eyelashes. Each of these conditions can incite or propagate the other; anterior blepharitis, if not treated, can lead to meibomian gland dysfunction (MGD) and vice versa. The standard treatment regimen consists of lid hygiene with warm compresses and eyelid scrubs, although these modalities may have limited efficacy for many patients, especially those with severe disease. Adjunctive treatment includes systemic and topical antibiotics, topical corticosteroids, and tear replacement therapy. Topical antibiotics are recommended to decrease the bacterial load, and topical corticosteroids may help in cases of severe inflammation.

Based on its well-known anti-infective profile, anti-inflammatory properties, excellent tissue penetration, and regulatory approval for the treatment of bacterial conjunctivitis, azithromycin ophthalmic solution 1% in DuraSite (AzaSite; Inspire Pharmaceuticals, Durham, NC) has been proposed as a novel treatment for posterior blepharitis.

**WHY AZITHROMYCIN?**

At present, there is no definitive FDA-approved treatment for either anterior or posterior blepharitis. The recently published International Workshop on MGD sponsored by the Tear Film & Ocular Surface Society, however, listed topical azithromycin as the first-line prescription pharmaceutical therapy in its algorithm for the treatment of MGD. In addition to its antibacterial properties, azithromycin—like erythromycin (another macrolide) and the tetracyclines—has been shown to have anti-inflammatory properties in several tissues throughout the body, including ocular tissue. Orally administered tetracyclines and macrolides have demonstrated efficacy in reducing inflammation in sebaceous glands, both in facial skin (in rosacea) and the lid margin, independent of their antibiotic effects. It was therefore suggested that topically applying azithromycin to the eye might also effectively treat blepharitis.

Several properties of azithromycin in DuraSite make this formulation well suited to the treatment of blepharitis. Most notably, the active drug can achieve high and sustained levels within eyelid tissue after topical administration. In addition, this broad-spectrum antibiotic has efficacy against the gram-positive organisms associated with blepharitis, it has a long half-life in eyelid tissue and it has anti-inflammatory properties.
RESEARCH

Several researchers have evaluated the efficacy of the off-label use of topical azithromycin for the treatment of blepharitis. One study compared topical azithromycin 1% combined with warm compresses to warm compresses alone for the treatment of posterior blepharitis.28 Unlike the compress-only group, the azithromycin group experienced a statistically significant improvement over baseline for lid margin redness (P < .001), meibomian gland plugging (P < .001), and quality of meibomian gland secretions (P < .001). Of interest, 44% of the patients in the azithromycin group but none in the compress-only group demonstrated a complete resolution of their meibomian gland plugging in at least one eye. Meibomian gland secretions normalized in almost a quarter of the patients in the azithromycin group after 2 weeks of therapy versus none in the compress-only group.

A second multicenter pilot study enrolled 76 patients with moderate-to-severe blepharitis.29 They were randomized to warm compresses alone or warm compresses and topical 1% azithromycin for a 4-week treatment period. At that point, investigators rated the efficacy of azithromycin as excellent or good in 70% of the patients in the azithromycin group compared with 48% in the compress-only group. More important, the positive improvements achieved in the azithromycin group persisted for as long as 2 weeks after therapy concluded.

In an open-label study of 26 patients with moderate-to-severe blepharitis, investigators evaluated changes in the clinical signs and symptoms of anterior and posterior blepharitis after a 4-week course of treatment with topical 1% azithromycin alone.30,31 Subjects were prohibited from using warm compresses in this study. Patient-rated symptom scores were all statistically significantly improved from baseline levels after 4 weeks of therapy (P < .001 for each symptom), and the improvement persisted for 4 weeks after therapy was stopped. These results supported the investigator-rated assessment of the clinical signs of blepharitis, which demonstrated statistically significant improvements in lid margin and conjunctival hyperemia, meibomian gland plugging, and ocular discharge after 4 weeks of therapy. These results persisted for 4 weeks after therapy ceased (last visit on day 57).

The aforementioned research suggests that topical azithromycin 1% may be effective as a stand-alone treatment for blepharitis and also as an adjunctive therapy with warm compresses. It also demonstrates that topical azithromycin more successfully treats the signs and symptoms of blepharitis than mechanical therapy (warm compresses) alone. These studies are limited, however, by their small size, open-label design, lack of a control arm, and potential bias due to the relationships of some of the investigators with the studies’ sponsors.

Foulks and colleagues evaluated the physical properties of the meibomian secretions in patients with MGD.32,33 The study demonstrated that the phase transition temperature and lipid ordering of the meibomian secretions trended toward normal after once-daily dosing of topical azithromycin for 4 weeks. The results correlate with the time course of the clinical improvements in the quality of the meibomian secretions noted in the previously mentioned studies. They also suggest that topical azithromycin may have a direct effect on the meibomian glands or their secretions.

Of note, two simultaneous, randomized, multicenter, double-masked, placebo-controlled phase 2 trials evaluated the effect on blepharitis of 2 and 4 weeks of topical azithromycin therapy (at clinicaltrials.gov, NCT00894530 and NCT00892970, respectively). These studies failed to meet their primary endpoint of the resolution of lid margin erythema, although several secondary outcome endpoints were achieved. Additional studies are planned.

CONCLUSION

The known antibacterial and anti-inflammatory aspects of topical azithromycin 1% in DuraSite and the promising results from early studies in patients with chronic blepharitis (both anterior and posterior) are encouraging. They warrant the drug’s recommendation by the TFOS Meibomian Gland Workshop as the first-line prescription pharmaceutical treatment for MGD and underscore the value that an off-label application based on strong science can bring to medicine. Further research in this area is warranted, and additional randomized, prospective, placebo-controlled trials are underway.

Jodi Luchs, MD, is an assistant clinical professor of ophthalmology at Hofstra University in Hempstead, New York. Dr. Luchs is the codirector of the Department of Refractive Surgery and the Cornea Service for the Long Island Jewish/North Shore University Health System in Great Neck, New York. He
is a consultant to Allergan, Inc.; Inspire Pharmaceuticals, Inc.; and Ista Pharmaceuticals, Inc. Dr. Luchs may be reached at (516) 785-3900; fluchs@aol.com.