A t present, there is no FDA-approved definitive treatment for anterior or posterior blepharitis. Because both the acute and chronic forms of the disease involve the presence of inflammation and bacteria, a comprehensive therapy that offers both antibiotic and anti-inflammatory properties coupled with good penetration into the lid tissue and convenient dosing might prove to be beneficial for this condition. Azithromycin ophthalmic solution 1% in Durasite (Azasite from Inspire Pharmaceuticals, Durasite from Insite Vision Incorporated) has been proposed as a novel treatment.

BACKGROUND
Azithromycin, like erythromycin (another macrolide) and doxycycline, has historically been shown to have anti-inflammatory properties and to improve clinical signs and symptoms of blepharitis after oral administration. An effective topical delivery system for azithromycin could provide the same benefits without the systemic side effects associated with oral administration. When azithromycin is delivered via Durasite, it binds to the mucin-coated surfaces of the eye (including the palpebral conjunctiva). The resulting formation of a sustained-release gel prolongs the availability and delivery of the drug on the ocular surface and enhances the agent’s penetration into the eyelids, conjunctiva, and cornea.

CURRENT STUDIES
Azasite is the only FDA-approved topical formulation of azithromycin available and marketed in the United States. It is indicated for the treatment of bacterial conjunctivitis. The research summarized in this section involves off-label uses of the medication.

Concentration
In several animal studies, after the topical administration of Azasite, high concentrations of the drug were present in ocular surface tissues. In one such study, when Azasite was administered according to the FDA-indicated dosing regimen for bacterial conjunctivitis (b.i.d. for 2 days, followed by q.d. for 5 days), peak concentrations of azithromycin in excess of 200 µg/g of tissue were achieved in eyelid tissue as the drug accumulated over the 7 days of therapy. Furthermore, 5 days after the medication’s discontinuation, tissue concentrations of azithromycin in excess of 50 µg/g were still present in the eyelids. Similar results were found for corneal and conjunctival samples in this study.

Another study involved humans scheduled to undergo cataract surgery who received Azasite b.i.d. for 2 days and then q.d. for an additional 5 days prior to surgery. Conjunctival biopsies were taken at the time of surgery in order to determine the concentration of azithromycin in the tissue. Similar to the animal studies, conjunctival concentrations of azithromycin in excess of 300 µg/mL were present after 7 days of therapy, with levels remaining above 50 µg/g 5 days after cessation of therapy (study reports 041-103, C-01-401-003, and C-01-401-004 on file with Inspire Pharmaceuticals, Inc.).

These animal and human studies suggest that the drug penetrates the ocular surface tissues in high concentrations and persists in therapeutic concentrations for several days after therapy is discontinued.

The high levels of azithromycin that can be achieved in ocular surface tissues, particularly the eyelids, after topical
administration and the degree to which they persist after discontinuation of the drug distinguish azithromycin from other commonly used topical antibiotics such as fluoroquinolones. For example, a postmarketing study compared Azasite 1% with moxifloxacin 0.5% (an ocular antibiotic commonly prescribed for the treatment of bacterial conjunctivitis) to determine the pharmacokinetic parameters of the drops after a single instillation into healthy human conjunctiva (N = 48). Tissue concentrations of azithromycin peaked 30 minutes after administration and remained elevated at therapeutic concentrations at 24 hours, whereas moxifloxacin’s concentrations peaked 2 hours after administration and were undetectable at 24 hours. These results illustrate the differences in tissue absorption and clearance between topical azithromycin and fluoroquinolones.6

Conversely, other studies have demonstrated that concentrations of moxifloxacin in the aqueous humor are significantly higher than those of azithromycin after topical administration.7 These results suggest that azithromycin tends to partition primarily within tissue, rather than aqueous solution, whereas fluoroquinolones such as moxifloxacin partition readily in aqueous solution.7

Efficacy

As noted earlier, azithromycin’s antibacterial and anti-inflammatory properties may make it a viable treatment option for chronic meibomian gland dysfunction. For that reason, this author recently performed a 2-week study comparing the efficacy of topical azithromycin 1% combined with warm compresses to that of warm compresses alone for the treatment of posterior blepharitis.8 In this study (N = 21), 10 patients were randomized to the combined therapy, and 11 received warm compresses alone. Patients in the azithromycin group experienced a statistically significant improvement from baseline in the extent of redness at the lid margin (P < .001), plugging of the meibomian gland (P < .001), and the quality of meibomian gland secretions (P < .001) (Figures 1-3). Patients in the warm compress-only group did not demonstrate a statistically significant improvement in any of these parameters. Of interest, the plugging in at least one eye completely resolved in 44% of the patients in the azithromycin group but none in the compress group. Moreover, almost one-quarter of the individuals in the azithromycin group but none in the compress group demonstrated a normalization of the meibomian gland’s secretions after 2 weeks of therapy. Adverse events (blurred vision, ocular irritation) were minor in the azithromycin group.

A multicenter pilot study9 enrolled 76 patients with moderate-to-severe blepharitis and randomized them to
treatment with warm compresses alone or warm compresses and topical 1% azithromycin for a 4-week period. At week 1, investigators rated the efficacy of azithromycin as excellent or good in 44% of patients in the azithromycin group, compared with only 15% in the compress-only group. These ratings increased to 70% in the azithromycin group and to 48% in the compress-only group after 4 weeks of therapy. More importantly, the positive improvements achieved in the azithromycin group persisted as long as 2 weeks after therapy had concluded.

An open-label study\(^{10,11}\) of 26 patients with moderate-to-severe blepharitis 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. Patients were prohibited from using warm compresses during this study. Patient-rated scores for itching, foreign body sensation, ocular dryness, ocular burning, and swollen eyelids all statistically significantly improved from baseline levels after 4 weeks of therapy (\(P < .001\) for each symptom). The improvement persisted for 4 weeks after the cessation of therapy. These findings supported the investigator-rated assessment of the clinical signs of blepharitis, which demonstrated statistically significant improvements in lid margin and conjunctival hyperemia, plugging of the meibomian gland, and ocular discharge following 4 weeks of therapy. The effect persisted for 4 weeks after the end of therapy (last visit on day 57).

These studies suggest that topical azithromycin 1% may be effective as a stand-alone treatment for blepharitis as well as for adjunctive therapy with warm compresses. The research shows that topical azithromycin is more successful at treating the signs and symptoms of blepharitis than just mechanical therapy (ie, 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 study’s sponsor.

Research by Foulks et al evaluated the physical properties of the meibomian secretions in patients with meibomian gland dysfunction.\(^{12}\) This study showed that the phase-transition temperature and lipid ordering of the meibomian secretions trended toward normalcy after once-daily dosing of topical azithromycin for 4 weeks. These 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 azithromycin may directly affect the meibomian glands or their secretions. Further study is warranted.

The described pilot studies prompted the initiation of larger, randomized, multicenter studies of the effect of topical azithromycin on blepharitis (more information available at http://clinicaltrials.gov). Two phase 2, randomized, double-masked, placebo-controlled studies of varying length (NCT00894530 and NCT00892970; 2 and 4 weeks, respectively) were recently completed and will evaluate both primary and secondary outcome measures in patients with blepharitis. Primary outcome measures are eyelid erythema, and secondary outcome measures include additional clinical signs and clinical symptoms of blepharitis.

**CONCLUSION**

The known antibacterial and anti-inflammatory aspects of topical azithromycin 1% in Durafine and the promising results from early studies involving subjects with chronic blepharitis (both anterior and posterior) are encouraging, although the results are limited by the study designs. Further research is warranted, and a randomized, prospective, placebo-controlled trial was recently completed. Blepharitis currently has no single approved treatment, its management is complicated, and it has wide-ranging signs and symptoms. For such a chronic and common disease, treatments that rapidly improve both clinical and self-reported signs and symptoms would be welcome.

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**Jodi Luchs, MD, is an assistant clinical professor of ophthalmology and visual sciences at Albert Einstein College of Medicine in Bronx, New York. Dr. Luchs is the director 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 Inspire Pharmaceuticals, Inc. Dr. Luchs may be reached at (516) 785-3900; jluchs@aol.com.**

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