

Treating Ocular Surface Disease

BY MALAIKA DAVID, ASSOCIATE EDITOR



This month's installment of the "Peer Review" column highlights the most recently published articles concerning diagnostic testing for and the therapeutic management of blepharitis. In a recent US survey, 34 million adults reported experiencing at least one of the three symptoms most commonly associated with blepharitis (redness, foreign body sensation, and itching), and only 4.5 million confirmed that they had received treatment for blepharitis.¹ The lack of relevant recent articles in peer-reviewed journals betrays the priority level accorded by ophthalmologists to successful outcomes in the management of this disease process. A look at patients' blogs and message boards reveals that many individuals with chronic blepharitis feel neglected by their treating physicians. All too often, we ophthalmologists tell these patients to start using warm compresses and lid scrubs and then send them on their way. If they return with complaints, many of us still prescribe erythromycin ointment, which is no longer the community standard and is clearly ineffective for the majority of patients.

As I mentioned in the July 2010 installment of this column, in order for us to be successful cataract and refractive surgeons, we must diagnose and treat ocular surface disease. Managing blepharitis and restoring the tear film require us to pay keen attention to the location of the tear film dysfunction and the source of ocular inflammation. Only then can we provide targeted treatment. A thoughtful compendium of therapeutic options by Katherine M. Mastrotta, MS, OD, was recently published in Cataract & Refractive Surgery Today's sister publication Advanced Ocular Care.²

Although the heart of this review centers on the use of topical azithromycin 1% in DuraSite (AzaSite; Inspire Pharmaceuticals, Inc.), I want to highlight a new treatment modality gaining some popularity in the management of dry eye syndrome and blepharitis. Intense pulsed-light therapy has been reported to improve patients' symptoms. Patients are treated with a double-pass technique, using the Quadra Q4 Platinum Intense Pulsed Light System (DermaMed International, Inc., Lenni, PA). Treatment settings range from 12 to 14 J/cm² with a pulse width of 20 ms. The goal is uniform, mild erythema of the treatment area without blistering or edema. Although no formal studies are available for review, DermaMed has reported an improvement in tear film breakup time as well as Schirmer's test scores, and the company is currently investigating this application in clinical trials. Finally, a topical interleukin-1 receptor antagonist is being investigated at the Massachusetts Eye and Ear Infirmary for the treatment of the signs and symptoms of posterior blepharitis.

I hope you enjoy this installment of "Peer Review," and I encourage you to seek out and review the articles in their entirety at your convenience.

—Mitchell C. Shultz, MD, section editor

CAUSES, SIGNS, AND SYMPTOMS OF BLEPHARITIS

Investigators analyzed four case studies to demonstrate the range of signs and symptoms that may be present in patients with blepharitis and factors that complicate its diagnosis and management. The patients included a 33-year-old man with anterior marginal blepharitis and lid margin notching; a 45-year-old man with conjunctivitis/blepharitis with eczema; a 65-year-old woman with meibomian gland dysfunction, rosacea, and dry eye; and a 72-year-old woman receiving prophylaxis for anterior segment surgery and concurrent blepharitis. The case studies were selected during a panel meeting of ophthalmologists with input from family doctors and an infectious disease/medical microbiologist. A Medline search was conducted to locate articles describing randomized controlled clinical trials, which served as evidence. Researchers found that blepharitis involving predominantly the skin and lashes tends to be staphylococcal and/or seborrheic in nature. Involvement of the meibomian glands was found to be seborrheic, obstructive, or a combination of the two. They noted that the pathophysiology of blepharitis is a complex interaction of factors such as abnormal lid-margin secretions, microbial organisms, and abnormalities of the tear film. They stated that blepharitis may present with a range of signs and symptoms and is associated with various dermatological conditions, including seborrheic dermatitis, rosacea, and eczema. The mainstay of treatment is a long-term regimen of eyelid hygiene. Topical antibiotics can be used to reduce the bacterial load, while topical corticosteroid preparations may be helpful for patients with marked inflammation.³

Investigators examined 10 patients with dry eye disease to determine the potential role of sPLA2-IIa (an enzyme reported to be in high concentration in tears) in chronic ocular surface inflammation. Human conjunctival epithelial cells were seeded in a 24-well plate and treated with placebo, sPLA2-IIa alone, TNF- α alone, or sPLA2-IIa and TNF- α . After 24 hours, the cells were harvested, and ribonucleic acid was isolated. The levels of inflammatory cytokine and chemokine production were detected by pathway-specific microarray technology. Investigators reported that sPLA2-IIa alone moderately stimulated the production of inflammatory cytokines and chemokines (CCL5, CCL25, IL-1-B, and IL-6); similar results were also drawn from the low concentration of TNF- α treatment. The combination of sPLA2-IIa and TNF- α resulted in a synergistic effect on the production of CCL5 and CCL25. Investigators then performed a quantitative real-time polymerase chain reac-

tion on CCL5 and CCL25. The expression of CCL5 and CCL25 messenger RNA increased significantly when sPLA2-IIa and TNF- α were added. Investigators concluded that these results confirm that sPLA2-IIa is an inflammatory mediator that can induce the inflammatory cytokine/chemokine production.⁴

TREATING BLEPHARITIS WITH AZITHROMYCIN

Luchs conducted a review of an off-label indication for topical azithromycin 1% in DuraSite for the treatment of blepharitis. He stated that the known antibacterial and anti-inflammatory aspects of topical azithromycin 1% in DuraSite and the promising results from early studies in subjects with chronic anterior and posterior blepharitis are encouraging. He further commented that the results are limited by study designs and additional studies are warranted. "In a chronic and common disease such as blepharitis that currently has no single approved treatment, is complicated in its management, and has wide-ranging signs and symptoms, treatments that rapidly improve both clinical and self-reported signs and symptoms are welcome."⁵

In a multicenter, open-label study, 26 patients with moderate-to-severe blepharitis received azithromycin ophthalmic solution 1% in the absence of warm compresses or eyelid scrubs for 28 days. Patients received the solution twice a day on the first and second days and once a day on the third through 28th day. Signs and symptoms were evaluated at baseline, the day after the treatment ended, and at 2 and 4 weeks posttreatment. Tear collection, bacterial cultures of the eyelid margin, and tear cytokines were measured by a multiplex immunobead assay. Investigators reported significant decreases from baseline in the signs of meibomian gland plugging, redness of the eyelid margin, palpebral conjunctival redness, and ocular discharge ($P \leq .002$) at day 29, which persisted for 4 weeks after treatment ($P \leq .006$). Patients also reported significant improvements in eyelid itching, foreign body sensation/sandiness/grittiness, ocular dryness, ocular burning/pain, and swollen/heavy eyelids from baseline ($P < .001$ for all symptoms and time points, except $P = .037$ for ocular dryness at the 4-week visit). Cultures of the eyelid margin revealed significant decreases in coagulase-negative staphylococci and *Corynebacterium xerosis* bacteria. No changes in tear cytokine concentrations were observed. Twelve subjects experienced 19 adverse events, 15 of which were ocular and none of which was serious.⁶

In a prospective, open-label study involving 150 eyes (75 patients) with chronic mixed anterior blepharitis, investigators tested the efficacy of azithromycin oph-

thalmic solution. Both eyes of each patient were treated with either azithromycin ophthalmic solution for 1.17 ± 0.49 months or erythromycin ophthalmic or topical ointment for a duration of 1.75 ± 1.39 months. At the initial visit, all patients underwent a slit-lamp examination and evaluation of the eyelids. At baseline, the mean blepharitis grade of all eyes was 2.15 ± 0.67 . By 4 weeks after treatment, 98.5% of the azithromycin group and 37.5% of the erythromycin group had achieved clinical resolution of their blepharitis. Eighty-seven percent of patients with chronic blepharitis were simultaneously found to have keratoconjunctivitis sicca. Fifty percent of patients treated with erythromycin required 8 weeks of therapy compared with 1.5% of patients treated with azithromycin.⁷

In a randomized, open-label study, 21 patients diagnosed with posterior blepharitis were randomized to receive either topical azithromycin ophthalmic solution 1% and warm compresses or warm compresses alone. The patients who received azithromycin applied one drop twice a day for 2 days followed by a once-daily drop for the next 12 days. All patients applied the compresses to each eye for 5 to 10 minutes twice a day for 14 days. Patients were evaluated for eyelid debris, red eyelids, swollen eyelids, meibomian gland plugging, and the quality of the meibomian gland's secretions on the first and last days of treatment. At the last visit, patients in the azithromycin group demonstrated significant improvements in plugging and secretions of the meibomian gland and redness of the eyelids when compared to the compress-only group. In the azithromycin group, plugging of the meibomian gland completely resolved in three patients, and the meibomian gland's secretions returned to normal in two patients. At the last visit, a higher percentage of patients in the azithromycin group rated overall symptomatic relief as excellent or good.⁸

TREATING ROSACEA WITH AZITHROMYCIN

In an open-labeled study, 18 patients with rosacea were assigned to receive 500 mg of oral azithromycin per day for 3 consecutive days each week for 4 weeks. Patients did not use any local measures for lid hygiene or any topical preparations during the study. Significant improvements occurred in ocular symptoms ($P = .002$), eyelid findings ($P < .0001$), and conjunctival hyperemia scores ($P = .005$). A therapeutic benefit was not observed in ocular surface staining scores. Baseline values of Schirmer's test results were within normal limits, and no significant side effects were observed.⁹

In a case series of ocular childhood rosacea, investigators highlighted three cases in which prolonged treat-

ment with oral erythromycin was administered. The patients included an 18-month-old girl with a 3-month history of facial pustules, a 3-year-old boy with a 7-month history of papular facial eruption associated with chalazia of the upper and lower eyelids, and a 12-month-old girl with a history of persistent, asymptomatic micropapular facial eruption associated with lesions of the upper eyelids. Investigators reported that the cases demonstrate the close association of periorificial dermatitis with childhood rosacea and highlight the importance of ocular signs to its diagnosis.¹⁰

FATTY ACIDS AND BLEPHARITIS

Joffre et al set out to determine if branched-chain fatty acids have a toxic effect on conjunctival cells related to blepharitis. Two human cell lines, a Wong-Kilbourne derivative of Chang conjunctival cell lines and the IOBA-NHC cell line, were treated with the branched-chain fatty acids isoC16 and isoC20 or palmitic acid as a control for 4 hours or 24 hours at 50 μm or 100 μm . Researchers investigated morphological and functional changes by measuring mitochondrial dehydrogenase activity, cellular permeability, mitochondrial depolarization, chromatin condensation, and IL-1 β and reactive oxygen species production. They noted that none of the fatty acids modified the parameters of cytotoxicity in conjunctival cells in the Chang or the IOBA-NHC cell lines. They further stated that only the mitochondrial dehydrogenase activity was significantly decreased in relation to the increased concentration of isoC20.¹¹ ■

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