Current Evidence for Topical Azithromycin 1% Ophthalmic Solution in the Treatment of Blepharitis and Blepharitis-Associated Ocular Dryness

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Introduction

Blepharitis, one of the most commonly treated ophthalmic conditions, can also be one of the most frustrating for the managing clinician. Although this is due in part to the chronic nature of the disease, the diversity of therapeutic options and lack of definitive scientific evidence for any single course of treatment also add significant challenge to clinical management.[1] Despite these difficulties, the prevalence of blepharitis and its role in dry eye or dysfunctional tear syndrome (DTS) make effective management of the disease essential to patient comfort and satisfaction. Azithromycin 1% ophthalmic solution (AzaSite: Inspire Pharmaceuticals), currently the Food and Drug Administration (FDA) approved for the treatment of conjunctivitis caused by susceptible isolates, has been investigated as a possible off-label treatment for chronic blepharitis. This study examines the current evidence for AzaSite as a treatment for chronic blepharitis and blepharitis-associated DTS.

Belpharitis Defined

The American Academy of Ophthalmology's[1] Preferred Practice Pattern defines blepharitis as a disease consisting of ''chronic ocular inflammation that involves the eyelid margin primarily and is a common cause of chronic ocular irritation.'' Blepharitis is typically divided into 2 subsets based on anterior or posterior eyelid involvement. Anterior blepharitis is primarily composed of staphylococcal and seborrheic disease, involving the eyelashes and associated glands. Posterior blepharitis, or meibomian gland dysfunction (MGD), involves the posterior

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lid margin and meibomian system.[1] In practice, blepharitis can be composed of exclusively anterior or posterior disease, or more often a combination of the 2. Despite the observed high prevalence of blepharitis in clinical practice, there is very little epidemiological evidence regarding its incidence or prevalence.

■ Signs and Symptoms of Blepharitis

Although symptoms and signs of blepharitis can vary significantly in both degree and course, the typical course of blepharitis is chronic with episodic exacerbations. Patient symptoms may range from mild chronic irritation including, itching, burning, and foreign body sensation, to more severe discomfort.[1] Chronic blepharitis and associated inflammation of the lid margin can lead to permanent changes including lid margin ulceration, eyelash loss and misdirection, lid margin thickening and scarring, and pathologic changes to meibomian gland orifices.[2–4] Alterations in the lid margin can subsequently deleteriously affect ocular surface health.[3] Secondary ocular surface involvement can manifest as surface inflammation, functional tear deficiency, and corneal pathology, ranging from punctuate epithelial erosions or marginal keratitis, to peripheral corneal thinning, neovascularization, and rarely perforation.[1] Finally, both anterior and posterior blepharitis can significantly reduce tear quality through degradation of the lipid component, thus further contributing to tear film dysfunction.[5,6] Interestingly, there is often a disconnect between visible signs and degree of symptoms in a patient with blepharitis. For example, younger patients are often very symptomatic with only minimal overt signs of disease; more aged patients may have extensive involvement and physical findings while being relatively asymptomatic. This lack of direct correlation between patient symptoms and degree of physical findings add challenges to blepharitis management, from diagnosis to quantification of symptomatic response to treatment.

■ Mechanism

At present, the mechanism of blepharitis is not clearly defined. This is in part due to the diversity of clinical findings and underlying etiologies but also may come from the difficulty of clearly differentiating affected individuals from controls on the basis of physical or laboratory findings. For example, the understanding of staphylococcal blepharitis is complicated by the ubiquitous presence of both *Staphylococcus epidermidis* and *Staphylococcus aureus* in both patients with blepharitis and normal controls.[7] There is, however, evidence that *S. aureus* is present at higher frequency in blepharitis-affected individuals, and that individuals with

blepharitis have higher lid margin bacterial loads when compared with controls.[8,9] Currently, proposed mechanisms of staphylococcal blepharitis include toxin related,[10] immunologic sensitization,[2] cell-mediated,[11] and antigen related.[12,13] In addition, a recently proposed mechanism attempts to correlate the observed higher lid margin bacterial load and related bacterial activity in blepharitis patients, with blepharitis findings.[9,10] This hypothesis, referred to as Quorum Sensing, invokes a "pathogenic communication system allowing bacteria to detect intraspecies and interspecies population levels" and in response, to increase certain proinflammatory virulence factors.[10] Thus, Quorum Sensing offers an explanation for the pathogenicity of otherwise ubiquitous and often innocuous skin flora.[14]

Staphylococcal blepharitis is thought to be infectious, whereas other forms of blepharitis are more commonly associated with systemic and inflammatory conditions. Both seborheic blepharitis and MGD are often associated with seborrheic dermatitis, and MGD is also associated with rosacea.[7,15] This correlation is very strong, with 1 study showing that 95% of individuals with seborrheic blepharitis also had seborrheic dermatitis.[7] Similarly, studies have shown high degrees of correlation between MGD and both seborrheic dermatitis (74%) and rosacea (51%).[7] These associations implicate a primarily inflammatory, rather than infectious etiology as with staphylococcal blepharitis. Although not an exhaustive listing of the proposed mechanisms of blepharitis, these examples illustrate multiple inflammatory and infectious hypotheses surrounding the various forms of this disease.

■ Blepharitis and DTS

Although the symptoms of blepharitis alone are certainly significant, it is important to also recognize that blepharitis often does not exist in isolation. This is particularly the case with respect to tear film dysfunction. As many as 25% to 40% of patients with seborrheic blepharitis and MGD have aqueous tear deficiency, a significant component of DTS.[7] Similarly, dry eye has been reported in up to 50% of patients with staphylococcal blepharitis.[7] Even in the absence of dry eye, tear breakup time has been shown to be significantly shorter in MGD.[16] Other studies have gone so far as to propose that "MGD represents the single most frequent cause of dry eye disease."[6] As Knop et al[3] illustrated in their recent publication, blepharitis associated changes to eyelid structure and function can have significant deleterious effects of ocular surface integrity and tear film function. Tear film physiology, specifically that of the lipid component, has been shown to be altered in blepharitis.[6] Cholesterol esters found in the tear film of individuals with chronic blepharitis may also serve as a stimulus for the proliferation of known blepharitis associated organisms.[17] In addition, *S. aureus* produces

lipolytic enzymes that break down esters and fats into fatty acids and glycerides, which may irritate the eye and destabilize the tear film.[17] Dry eye patients have also been shown to have decreased phospholipid composition of their meibomian secretions, which may have a destabilizing effect on the tear film.[18–20] Structurally, the nonkeratinized posterior lid margin can be altered or damaged in chronic blepharitis, which can be detrimental to ocular surface health, given this region's essential role in tear film distribution and ocular surface maintenance.[3] Finally, DTS both in posterior blepharitis and in isolation has been found to be associated with ocular surface inflammation, as demonstrated by significantly increased tear cytokines and chemokines.[21]

■ Current Management Strategies

The deleterious implications of lid margin changes in ocular surface health, and the role of chronic blepharitis in inducing these changes, further stresses the importance of the successful management of blepharitis. Unfortunately, there is not sufficient evidence to allow for definitive treatment recommendations for blepharitis.[22] The lack of adequately proven treatment may again relate to the difficulty in clearly defining those with blepharitis and in the frequent disconnect between signs and symptoms of the disease as discussed previously. Current management strategies of blepharitis are primarily derived from level III evidence and include a combination of mechanical removal of blepharitis material, warm compresses for management of meibomian dysfunction, antibiotics (topical or oral) and/or topical anti-inflammatory agents.[1] The foundation of anterior blepharitis treatment is mechanical removal of scales, deposits, and crusts with either dilute "no-tears" shampoo or a number of commercially available lid hygiene products.[1] This may be performed in isolation or in conjunction with warm compress application, the most common current MGD management strategy, which is thought to both soften encrustations and warm the meibomian secretions. Some practitioners prescribe topical antibiotics ointments including bacitracin or erythromycin with varying frequency to manage the presumed infectious component of the disease. In addition, oral tetracyclines such as doxycycline and minocycline can be utilized for the treatment of inflammatory lid margin disease and posterior blepharitis, primarily for their anti-inflammatory properties.[1] Tetracycline use is limited by its common side effects including sun sensitivity and gastrointestinal upset and also known contraindications to use in pregnant women and children. Macrolide antibiotics, like erythromycin and azithromycin, also are shown to have anti-inflammatory activity.[23] In cases with more severe lid margin inflammation, some practitioners utilize short-term topical corticosteroid therapy to more rapidly improve lid margin inflammation and symptoms.[1] Finally,

symptomatic relief can be accomplished with artificial lubrication, in either drop or more viscous form, particularly for those patients with a dysfunctional tear component. As should be evident from the diversity of options discussed above, blepharitis treatment regimens can be quite onerous and confusing, leading to poor patient compliance.

■ Blepharitis in DTS/Dry Eye Guidelines

Of specific interest to this study is the role of blepharitis in DTS. Currently, 2 of the most widely used guidelines for the diagnosis and management of DTS or dry eye syndrome come from the 2006 publication of the Delphi panel's consensus on DTS and the 2008 Preferred Practice Pattern on Dry Eye Syndrome from the American Academy of Ophthalmology.[24,25] Although these guidelines span a much wider spectrum of the disease, blepharitis as a component of DTS is addressed by both. As discussed previously, blepharitis and DTS frequently occur concurrently, likely due to the causative relationship outlined above, in addition to the fact that both occur with a relatively high prevalence in elderly patients. Both of the aforementioned guidelines address the role of blepharitis in dry eye and the need to treat blepharitis as part of dry eye management. The Delphi panel divided DTS into 2 groups: DTS with lid margin involvement and DTS without lid margin involvement. Those cases falling in the "with lid margin involvement" group were further subdivided into primarily "anterior" or "posterior" disease. The suggested intervention for anterior blepharitis in DTS was lid hygiene and antibacterial therapy (unspecified). Recommended management of posterior blepharitis, or MGD, consisted of warm massage, oral tetracyclines, and topical steroids as needed.[24] The 2008 Preferred Practice Patterns subdivided dry eyes using the definitions of the International Dry Eye Workshop, which breaks the disease down into 3 groups by major etiology: "aqueous-deficient," "evaporative" or a combination of the 2. Within the "intrinsic" subgroup of "evaporative" disease, meibomian gland involvement was implicated, primarily due to the lipid tear phase changes discussed previously. Proposed blepharitis management was based on disease severity and similarly included lid hygiene and warm compresses in mild disease. In moderate or severe cases, topical anti-inflammatory agents (cyclosporine and steroids), oral tetracyclines, systemic anti-inflammatory agents, and oral ω-3 fatty acids were advised.[25] Although these 2 studies address the role of blepharitis in DTS and suggest treatment options, their suggested management is no more straightforward than the diverse options discussed in the current management section of this article.

■ Topical Azithromycin Ophthalmic

Azithromycin ophthalmic solution 1% (AzaSite: Inspire Pharmaceuticals) is a topical form of azithromycin, a broad spectrum macrolide

antibiotic available in oral form in the United States since 1992. Topical azithromycin currently has an FDA indication for the treatment of bacterial conjunctivitis caused by susceptible isolates.[26] Although this ophthalmic formulation of azithromycin was predated by erythromycin ophthalmic, another macrolide antibiotic previously mentioned as a treatment option for blepharitis, topical azithromycin is felt to have a number of treatment advantages compared with erythromycin. Specifically, azithromycin has a broader spectrum of activity than erythromycin,[27] increased tissue penetration, and a longer elimination half-life.[28] In addition, azithromycin's mechanism of action (50 S ribosomal inhibition) and pharmacokinetics allow daily dosing, as opposed to the more frequent dosing of erythromycin.[29] Finally, AzaSite in particular utilizes a unique bioadhesive matrix application that not only helps stabilize azithromycin on the ocular surface and lids but also facilitates sustained delivery of the drug.[29] These characteristics of broad efficacy spectrum, good tissue distribution to lid tissue, favorable pharmacokinetics, and a sustained release delivery system make topical azithromycin ideal for management of the bacterial component of blepharitis.

An additional advantage of topical azithromycin is its known potent anti-inflammatory properties. Early evidence of azithromycin's anti-inflammatory activity comes from its use in the management of pulmonary conditions such as panbronchiolitis, bronchiolitis obliterans, and asthma, in which azithromycin was demonstrated to induce reductions in airway inflammation.[30,31] Specifically, azithromycin has been shown to suppress activation of NF-κB, and therefore elicit a subsequent decrease in inflammatory cytokine levels such as interleukin-6 (IL-6) and IL-8.[32] Recently published research on the anti-inflammatory properties of azithromycin in ocular tissues also demonstrate decreased corneal inflammation and inflammatory cytokines in a murine model of corneal inflammation treated with topical azithromycin.[33] More specifically, it demonstrated decreased corneal leukocyte infiltration, decreased messenger RNA expression of Interleukin-1β, tissue necrosis factor-α, and intercellular adhesion molecule-1 in the cornea of mice with thermal cautery induced corneal inflammation when compared with vehicle alone.[33] This is significant, as tissue necrosis factor-α along with other inflammatory cytokines, have been demonstrated to be increased in DTS, both with and without meibomian dysfunction.[21] Azithromycin's proven anti-inflammatory effects in pulmonary medicine combined with recent studies, suggesting a reduction of ocular inflammation in a murine model of corneal disease further strengthen the rationale for its use in blepharitis management.

■ AzaSite Treatment Trials for Management of Blepharitis

Since the introduction of AzaSite, a number of groups have investigated its efficacy in the management of blepharitis and associated

symptoms. Haque et al[34] (Cornea, Aug 2010) treated 26 patients with moderate to severe blepharitis with azithromycin ophthalmic 1% for 28 days in a multicenter open label study, in the absence of lid scrubs or lid hygiene therapy. In doing so, they demonstrated significant decreases in physical signs of MGD including "gland plugging, eyelid margin redness, palpebral conjunctival redness, and ocular discharge ($P < 0.002$)." Importantly, they also noted statistically significant improvement in patient reported symptoms such as itching, foreign body sensation, ocular dryness, burning, pain, and heaviness at weeks 4, 6, and 8 ($P < 0.001$) with the only exception being ocular dryness at the fourth week visit ($P = 0.037$). The 6 and 8 week time points demonstrated maintenance of improvement up to 28 days after completion of therapy. Eyelid margin culture also exhibited decreases in coagulase-negative streptococci and *Corynebacterium xerosis*. Interestingly, the Haque study was unable to show measurable change in tear film cytokine levels. This is in contrast to experimental evidence from the murine model discussed previously.[33] This discrepancy may be due to the fact that in the mouse model the polymerase chain reaction and flow cytometry were performed on corneal tissue from killed mice, whereas Haque's analysis was done by cytokine assay of tear samples.[33,34]

A similar a study in the Optometric literature (Opitz, Clinical and Experimental Optometry 2010) completed a 30 day open label trial of 1% azithromycin for management of posterior blepharitis, looking at pretreatment and posttreatment physical findings. This study also addressed symptomatic improvement in dry eye symptoms using the Ocular Surface Disease Index, a scientifically validated questionnaire used by researchers to measure severity of dry eye symptoms. Topical azithromycin demonstrated statistically significant improvement in both tear break up time (52.7% increase) and Schirmer testing (24% increase). Conjunctival staining decreased 67.9% ($P<0.0001$) and corneal staining decreased 83.2% ($P<0.0001$). The patients' lid margin scores were also reduced by 33.9% ($P<0.0001$). Most importantly Ocular Surface Disease Index scores improved 61.8% from baseline, meaning that patients experienced significant symptomatic improvement in addition to the observed improvement in physical markers of disease.[35]

Finally, Luchs[36] performed a 14-day open label study with 21 participants comparing 1% azithromycin combined with warm compresses, versus warm compresses alone. This study demonstrated significant benefit the combined Azasite treatment compared with warm compresses alone. Specifically, the combination group showed improvement in meibomian gland plugging ($P < 0.001$), meibomian secretions ($P < 0.001$), and eyelid redness ($P < 0.001$) when compared with the control group. In addition, a higher percentage of combination treated patient rated their symptomatic improvement as excellent or good when

compared with the warm compress alone group ($P = 0.024$). There was no demonstrated difference in lid debris, swelling, or acuity.

In summary, these 3 representative studies, while not level I evidence, do support the use of daily topical Azasite for improvement of physical findings and symptoms of blepharitis. Importantly, they also demonstrate concurrent reduction in related dry eye signs and symptoms, without significant treatment side effects.[36] AzaSite therapy, as completed in these studies, clearly resulted in the reduction of the signs and symptoms of blepharitis and dry eye findings, with 1 study showing a sustained effect lasting at least 4 weeks after discontinuation of therapy.[34]

■ Treatment Recommendations for Blepharitis

On the basis of the information known to date regarding the use of AzaSite for blepharitis, we feel that the following management recommendations are advisable. In the management of mild-to-moderate anterior blepharitis, a patient should first be advised to initiate a regimen of twice daily warm compresses and lid hygiene to aid in physical removal of debris. If after a period of 2 to 3 weeks this is not effective, a topical antibiotic ointment should be added (Polymyxin B/Trimethoprim or comparable) with three times a day dosing. Of note, if there is physical evidence of significant bacterial burden at initiation of treatment such as lash colarettes, the physician may elect to use an antibiotic ointment from the outset. If the initial topical antibiotic is ineffective, it should be discontinued in favor of a trial of topical azithromycin 1%. Dosing should follow the most frequently cited regimen of two times a day for the first 2 days, followed by daily application, directly to the lashes, for a total of 28 days. At the 28 day time point, the patient should be reevaluated. On the basis of observed clinical response, AzaSite therapy can be continued for an additional 4 weeks. If after 2 rounds of azithromycin of therapy the patient has not achieved control of signs and symptoms of blepharitis, therapy should be escalated further to include oral doxycycline therapy, if not contraindicated. For posterior blepharitis, a similar stepwise approach is advisable; however, lid scrubs can be excluded if there is an absence of anterior disease. This stepwise approach will simplify management of blepharitis for the treating physician and allows a trial of less costly management strategies before initiation of AzaSite. This is reasonable in light of the significant additional cost of AzaSite ($90.99 per 2.5 mL) compared with erythromycin ophthalmic ($13.99 per 3.5 g tube).[37] In addition, treatment failure of alternate topical antibiotic therapy may have the practical effect of increasing the likelihood that AzaSite would be covered by a patient's insurance provider. Any successful blepharitis regimen must include adequate patient education regarding the chronic nature of this disease and the need for daily therapy over an extended period to gain symptomatic control.

■ Conclusions

Although there is no shortage of treatment options for blepharitis, this analysis proposes that topic azithromycin 1% (AzaSite) represents a useful tool in the treatment of both blepharitis and blepharitis-associated dry eye disease. The theoretical benefits of topical azithromycin treatment in blepharitis, due to its antibiotic and anti-inflammatory properties, have been substantiated through a number of clinical and scientific investigations. In addition, topical azithromycin, specifically in the AzaSite formulation, has a number of unique advantages including once-daily dosing and a better side effect profile than other similar medications. These factors make topical azithromycin 1% an ideal choice for the management of mild to moderate blepharitis after initial therapy has proven ineffective.

The authors declare that they have no conflicts of interest to disclose.

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