Review of Azithromycin Ophthalmic 1% Solution (AzaSite®) for the Treatment of Ocular Infections

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Abstract: AzaSite® (azithromycin 1.0%) ophthalmic solution was approved in 2007 by the US Food and Drug Administration (FDA) as the first commercially available formulation of ophthalmic azithromycin for the treatment of bacterial conjunctivitis. AzaSite® utilizes a vehicle delivery system called DuraSite®, which stabilizes and sustains the release of azithromycin to the ocular surface, leading to a longer drug residence time, less frequent dosing, and an increase in patient compliance. AzaSite® is a broad spectrum antibiotic, effective against Gram-positive, Gram-negative, and atypical bacteria. AzaSite® has been studied for the treatment of ocular conditions beyond its clinical indication. A number of clinical studies have evaluated its efficacy and safety in the management of ocular conditions such as bacterial conjunctivitis and blepharitis on both the pediatric and adult populations. This article aims to evaluate the peer-reviewed published literature on the use of azithromycin 1.0% ophthalmic for current and possible future ophthalmic uses.

Keywords: azithromycin, AzaSite®, DuraSite®, bacterial conjunctivitis, blepharitis
Introduction

Azithromycin is a semi-synthetic macrolide antibiotic derived from and similar in structure to erythromycin. Azithromycin differs chemically from erythromycin by the inclusion of nitrogen-methyl group in the lactone ring that improves the stability of the drug in acidic environments. Azithromycin has a longer serum half-life, improved bioavailability, increased tissue penetration and persistence than erythromycin.1

The antibacterial effect of azithromycin occurs by binding to the 50S subunit of the 70S bacterial ribosome and inhibiting RNA-dependent protein synthesis within the bacteria.1 Azithromycin is transported to bacteria via phagocytic cells and fibroblasts which carry the drug on their way to the site of infection. Once at the site of infection, large concentrations of azithromycin are slowly released by exposure of the phagocyte to the cell membrane of the bacteria where ribosomal binding occurs.2,3 It is the ribosomal binding that contributes to bacteria death or inhibits bacteria growth depending on the organism, its sensitivity to azithromycin, and the concentration of azithromycin in the infected tissue. The average terminal half-life of elimination of the oral preparation of azithromycin is 68 hours.4

Azithromycin is a broad spectrum antibiotic that has been shown to be effective against Gram-positive, Gram-negative, and atypical bacteria including Hemophilus influenza, Staphylococcus aureus, Streptococcus mitis group, Streptococcus pneumoniae, and CDC coryneform group G.5 When administered systemically, high tissue concentrations of azithromycin have been found in the ocular tissues such as the conjunctiva, iris, ciliary body, and eyelid which is why systemically administered azithromycin is an effective treatment for the ocular infection of Chlamydia trachomatis.6,7 Lesser concentrations have been found in the aqueous and vitreous humors at levels below the minimum inhibitory concentration8–10 which make it a less favorable therapeutic option for intra-ocular infections of the anterior or posterior chambers of the eye.

In addition to its broad spectrum antimicrobial activity, azithromycin demonstrates anti-inflammatory and immunomodulatory properties. Although the anti-inflammatory and immunomodulatory effects overlap, the oral formulation of azithromycin is thought to suppress the production of pro-inflammatory mediators such as cytokines (TNFα and IL-1β), chemokines, and matrix metalloproteinases (MMP-1, MMP-3, and MMP-9).11–13 The combined antimicrobial and anti-inflammatory effect of azithromycin makes it a particularly interesting treatment option especially for bacteria capable of producing an inflammatory response that could be destructive to the host tissue.

Despite the antimicrobial and anti-inflammatory effects demonstrated in the systemic preparation of azithromycin, many ophthalmic clinical situations would benefit from topical administration of azithromycin to minimize potential systemic side effects, and to target azithromycin to the site of ophthalmic infection. Commercially available azithromycin 1.0% ophthalmic solution (AzaSite®) is available for the treatment of bacterial conjunctivitis caused by susceptible isolates.14,15 AzaSite® has been studied for the treatment of ocular infections and ocular diseases beyond its clinical indication. We reviewed the peer-reviewed literature to report on the use of topical ophthalmic azithromycin 1% for ophthalmic uses. We also included a review of some unpublished studies found in the Cochrane Register of Clinical Trials and clinicaltrials.gov.

Pharmacokinetics

In 2007, the US Food and Drug Administration (FDA) approved the first ophthalmic formulation of azithromycin which is commercially available as azithromycin 1.0% ophthalmic solution (AzaSite®).14 AzaSite® utilizes a vehicle delivery system called DuraSite®, a proprietary polymeric mucoadhesive delivery system which stabilizes and sustains the release of azithromycin to the ocular surface. This polymeric mucoadhesive delivery system also known as a polycarbophil bioadhesiveness is created by crosslinking polymer chains that bond with glycosaminoglycans found in mucus.16 DuraSite® solubilizes azithromycin at a high concentration and protects it from degradation during manufacturing and storage.17 It also retards the loss of drug that can occur by tear turnover, lacrimation and dilution by releasing the drug over a period of time in a predictable manner.

The physical nature of DuraSite® also enables it to retain hydrophobic molecules such as drugs like azithromycin and release them onto the ocular surface over a sustained period.15 In one study, the effectiveness of azithromycin 1.0% with and without polycarbophil
Azithromycin 1% ophthalmic solution

(DuraSite®) was compared in rabbits. This study showed peak drug concentrations in the tear film, cornea, conjunctiva and eyelids were higher when azithromycin was used with polycarbophil rather than without as demonstrated by the area under the curve (AUC). The sustained effect of azithromycin with polycarbophil after discontinuation of the medication exhibited concentration levels above the minimum inhibitory concentrations (MICs) for at least 6 days following the last dosing. The half-lives in conjunctiva and cornea were 63 and 67 hours, respectively. This was consistent with half-lives seen in the same tissues when azithromycin is administered systemically. In this same study, aqueous humor concentrations were also evaluated. Although the concentration levels of azithromycin were higher when dosed with polycarbophil rather than without, the concentration levels were considered below MIC levels.

Another study using human subjects, evaluated the aqueous humor and conjunctival pharmacokinetics of commercially available azithromycin 1.0% both during and after 7 day dosing regimen with twice daily dosing for 2 days followed by once daily dosing for 5 days. Peak conjunctival levels of azithromycin were achieved after 48 hours of twice-daily dosing and reached a measured level of 559.7 µg/g. In this study, azithromycin levels in the conjunctiva continued to remain above the MIC90 for an additional 7 days after discontinuation of the therapy. The elimination half-life of azithromycin in conjunctival tissue after topical dosing was 65.7 hours which was also found in the systemic administration. Azithromycin 1.0% was 100-fold less than the MIC90 in the aqueous humor as was also similar to the oral administration.

Concentration levels of azithromycin 1.0% and moxifloxacin 0.5% ophthalmic solutions in the conjunctiva of healthy adults were evaluated in 48 patients after receiving a single dose of either medication. Conjunctival biopsy samples were evaluated at 30 minutes or 2, 12, or 24 hours after administration. Study results showed that after a single dose of topical azithromycin 1.0%, concentration levels were highest at 30 minutes after administration and remained at high therapeutic levels for 24 hours after instillation. After a single dose of moxifloxacin, peak concentration levels were at 2 hours after instillation and were undetectable after 24 hours.

The high conjunctival concentration of topically instilled azithromycin 1.0% in DuraSite® is thought to be partly due to the long contact time and high tear concentrations. Tear concentrations after topical administration of 0.5%, 1.0% and 1.5% azithromycin in 91 healthy volunteers was evaluated in another study. Subjects were randomized and received one drop of either 0.5%, 1.0%, or 1.5% topical azithromycin solution. Tear concentrations were measured at seven time points for 24 hours. Once daily administration of 1.0% and 1.5% azithromycin were shown to reach areas under the inhibitory curve (AUC) above the required threshold for antibacterial activity against Gram-positive bacteria, suggesting a twice daily instillation is more likely to ensure antimicrobial activity against Gram-negative bacteria.

Despite the broad spectrum antimicrobial effects and sustained high therapeutic concentration levels, oral macrolide antibiotics have been historically characterized as bacteriostatic where the drug inhibits the bacterial growth rather than killing bacteria as in bactericidal antibiotics. This was further investigated in a kinetics-to-kill model azithromycin 1.0% which confirmed the bacteriostatic effects even at peak concentration levels in the conjunctiva. These results lead to concerns of bacterial resistance which is more common among bacteriostatic agents rather than bacteriocidal agents. Further, it has also been suggested that microorganisms residing in biofilms are often between 20 and 1,000 times more resistant to antibiotics than genetically identical bacteria living as free floating cells. Biofilms are organized communities of bacteria and are more resistant to host defenses, often difficult to culture, and associated with chronic diseases. A study analyzed the effect of azithromycin 1.0% in DuraSite® on biofilm formation by Staphylococcus aureus and coagulase-negative staphylococci in vitro. Results showed that Azasite® inhibits biofilm formation by reduction of bacterial growth which could reduce resistance despite the bacteriostatic nature of the drug.

In addition to its bacteriostatic antibiotic effects, azithromycin has demonstrated anti-inflammatory and immunomodulatory activity especially in the presence of microbial infections. Ocular surface inflammation is characterized by increased levels of inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α. The ocular anti-inflammatory effects of
azithromycin on the production of proinflammatory mediators in cultured human corneal epithelial cells stimulated with zymosan were studied. The results demonstrated that azithromycin suppresses the stimulation of proinflammatory responses by blocking NF-κB activation. This suppression of NF-κB, decreases the levels of proinflammatory cytokine IL-6 and IL-8 which could be helpful in the treatment of certain inflammatory ocular surface diseases. In another study, the effect of topical azithromycin was studied in a murine corneal inflammation which was induced by thermal cautery. In this study, topical azithromycin significantly reduced leukocyte infiltration into the cornea. In the same study, there was a decrease expression of IL-1β, TNF-α, and ICAM-1 in the cornea indicating azithromycin may have a potential anti-inflammatory effect on corneal inflammation. An immunomodulatory effect occurs as azithromycin enhances the production of IL-10 which is an immunomodulatory cytokine produced by activated macrophages and some lymphocytes. Once the immunomodulator cytokine IL-10 is produced, IL-10 inhibits the inflammatory cytokines (IL-1 and TNF) involved in the inflammatory response seen with ocular surface inflammation.

Clinical Uses
Pharmacokinetics studies (absorption, metabolism, distribution, and excretion) of azithromycin 1.0% in DuraSite® demonstrate effective anti-microbial and anti-inflammatory activity with high sustained tissue concentrations in the conjunctiva, cornea, tear film and eyelids. Since the US FDA approval of AzaSite® in 2007, a number of clinical studies have evaluated its efficacy in the management of ocular conditions such as bacterial conjunctivitis and blepharitis. Our discussion below focuses primarily on the 1% formulation of azithromycin ophthalmic solution, but Table 1 summarizes the published clinical studies on the applications of both 1.0% azithromycin and the 1.5% European formulation for the treatment of bacterial conjunctivitis, blepharitis, and pediatric use.

Bacterial conjunctivitis
Although most bacterial conjunctivitis is self-limiting, most advocate the use of topical antibiotics to provide symptomatic relief, hasten microbial remission, shorten disease duration, reduce the risk of developing sight threatening complications, reduce recurrence rates, and prevent the spread of infection. During review of the clinical trials, we found three trials that collectively enrolled over 1600 patients to study the effectiveness of commercially available azithromycin 1.0% ophthalmic solution (AzaSite®) in the treatment of bacterial conjunctivitis. The first was a phase 3 prospective, randomized clinical trial that included 743 subjects from the age of one to ninety-six who were diagnosed with bacterial conjunctivitis. Patients were treated with azithromycin 1.0% in DuraSite® or tobramycin 0.3%. Out of the 743 patients, 96% of the patients completed the trial. Azithromycin 1.0% dosed twice daily for 2 days then once daily for 3 days achieved a similar safety profile to that of tobramycin 0.3% when dosed four times a day for 5 days. This study showed that azithromycin 1.0% was well tolerated in subjects of all ages (one year of age and older) and that rates of bacterial eradication were the same for both treatment groups.

In a second prospective, randomized, vehicle-controlled, double-masked, parallel-group, multicenter clinical trial of 630 patients, the efficacy of azithromycin 1.0% in DuraSite® was compared with its vehicle in a five day course of treatment for bacterial conjunctivitis. Overall, azithromycin 1.0% in DuraSite® eradicated 85% of the azithromycin-resistant pathogens isolated, including 92% of S. pneumoniae strains. The overall eradication rate for azithromycin ophthalmic solution against bacteria with MIC of > 1024 µg/mL was 78% (67% for S. aureus and 100% for S. epidermidis, S. pneumoniae, and S. mitis). In a third randomized, phase 3 clinical trial conducted at 47 sites, the efficacy of azithromycin 1.0% in DuraSite® was compared to 0.3% tobramycin ophthalmic solution for the treatment of bacterial conjunctivitis. Patients either received azithromycin 1.0% in DuraSite® dosed twice daily on days 1 and 2 then once daily through day 5, or 0.3% tobramycin dosed 4 times daily for 5 days. Results of this study demonstrated clinical resolution in 79.9% of subjects who received azithromycin 1.0% as compared to 78.3% of subjects who received 0.3% tobramycin. This study also showed bacterial eradication of 88.1% in the azithromycin group as compared to 94.3% in the tobramycin group. Overall, results of this study indicated that the efficacy rates
Table 1. Summary of results from clinical studies of topically administered azithromycin in the treatment of bacterial conjunctivitis, blepharitis/mebomian gland dysfunction, and pediatric use.

| Reference          | Treatment type                                                                 | No. of pts (duration) | Treatment groups                  | Results                                                                 |
|--------------------|--------------------------------------------------------------------------------|-----------------------|-----------------------------------|------------------------------------------------------------------------|
| **Bacterial conjunctivitis** |                                                                                     |                       |                                   |                                                                         |
| Abelson et al32    | Azithromycin 1.0% ophthalmic solution in DuraSite® on bacterial conjunctivitis     | 630 age 1 to 96 (5d)  | Azithromycin 1.0% in DuraSite® vs.  | Clinical resolution with azithromycin in DuraSite® was statistically     |
|                    |                                                                                     |                       | vehicle Dosage: twice daily on    | significant compared to that of the vehicle (P = 0.030) at visit 3.    |
|                    |                                                                                     |                       | days 1 and 2 and once daily on    | Bacterial eradication rates with azithromycin ophthalmic solution      |
|                    |                                                                                     |                       | days 3–5                          | reached 88.5% at visit 3 (P < 0.001). Adverse events include: ocular   |
|                    |                                                                                     |                       |                                  | irritation, conjunctival hyperemia, worsening of the condition         |
|                    |                                                                                     |                       |                                  | Rate of bacterial resolution: 85.2% for azithromycin, 83.8% for        |
|                    |                                                                                     |                       |                                  | tobramycin on day 3; 92.8% for azithromycin, 94.6% for tobramycin on   |
|                    |                                                                                     |                       |                                  | day 9. Azithromycin was demonstrated to be non-inferior to tobramycin   |
|                    |                                                                                     |                       |                                  | at both timeframes                                                     |
|                    |                                                                                     |                       |                                  | 96% of patients completed the trial. Both study medications were well   |
|                    |                                                                                     |                       |                                  | tolerated. Azithromycin 1.0% dosed twice daily for 2 days then once   |
|                    |                                                                                     |                       |                                  | daily for 3 days achieved a safety profile similar to tobramycin dosed  |
|                    |                                                                                     |                       |                                  | 4 times a day for 5 days. Azithromycin 1.0% was well tolerated in       |
|                    |                                                                                     |                       |                                  | patients 1 year of age and older. Rates of bacterial eradication were   |
|                    |                                                                                     |                       |                                  | the same in both groups                                               |
|                    |                                                                                     |                       |                                  | Clinical resolution was observed in 79.9% of subjects in the           |
|                    |                                                                                     |                       |                                  | azithromycin group and 78.3% of subjects who received tobramycin.      |
|                    |                                                                                     |                       |                                  | Bacterial eradication was 88.1% for azithromycin and 94.3% for         |
|                    |                                                                                     |                       |                                  | tobramycin. Efficacy of tobramycin 0.3% and 1% azithromycin are         |
|                    |                                                                                     |                       |                                  | equivalent. Azithromycin 1.0% in DuraSite® provides effective antibiotic |
|                    |                                                                                     |                       |                                  | coverage against most bacteria seen with bacterial conjunctivitis      |
| Denis et al48      | Topically applied azithromycin 1.5% compared to tobramycin 0.3% for purulent bacterial conjunctivitis | 1043 adults and children (n = 524) (3d) | Azithromycin 1.5% twice daily for 3 days vs. tobramycin 0.3% every 2 hours while awake for 2 days, then four times daily for 5 days |                                                                         |
| Protzko et al31    | Azithromycin 1.0% in a polymeric mucoadhesive delivery system with 0.3% tobramycin ophthalmic solution for treating bacterial conjunctivitis | 743 age one to 96 (5d) (n = 343/365) | Azithromycin 1.0% in DuraSite® vs. tobramycin 0.3%. Dosage: azithromycin 1.0% in DuraSite® twice daily for days 1 and 2 and once daily on days 3 to 5; 0.3% tobramycin four times daily for 5 days |                                                                         |
| Abelson et al32    | Efficacy of azithromycin 1.0% in DuraSite® compared to 0.3% tobramycin for the treatment of bacterial conjunctivitis in adult and pediatric subjects | Azithromycin (n = 159) Tobraimycin (n = 157) Age 1 year and older 5d | Subjects were randomized to either receive azithromycin 1.0% in DuraSite® or 0.3% tobramycin. Azithromycin was dosed once dosed twice daily for days 1 and 2 and once daily on days 3 through 5. Tobramycin was dosed 4 times daily for 5 days |                                                                         |

(Continued)
Table 1. (Continued)

| Reference | Treatment type | No. of pts (duration) | Treatment groups | Results |
|-----------|----------------|-----------------------|------------------|---------|
| **Blepharitis** | | | | A statistically significant lower mean global score \((P = 0.0002)\) was observed in subjects treated with ST compared to subjects treated with Azasite® at day 8. No serious adverse events were reported in either group. |
| Torkildsen et al⁴⁰ | Tobramycin/dexamethasone ophthalmic suspension (Tobradex ST®) 0.3%/0.05% compared to azithromycin 1.0% (Azasite®) ophthalmic solution in the treatment of moderate to severe blepharitis/blepharoconjunctivitis | 122 (14d) Azasite (n = 61) Tobradex ST (n = 61) | Patients were randomized to either receive one drop of ST four times daily for 14 days vs. one drop of Azasite® dosed twice daily for 2 days then once daily for 12 days | |

| John T³⁵ | Topical administration of azithromycin versus erythromycin for the treatment of chronic mixed anterior blepharitis | 75 Azithromycin (1.17 ± 0.49 months) Erythromycin (1.75 ± 1.39 months) Azithromycin (n = 67) Erythromycin (n = 8) | Azithromycin ophthalmic solution vs. erythromycin ophthalmic ointment | 66 of the 67 patients who used azithromycin showed complete recovery. Clinical resolution after four weeks was 98.5% for azithromycin and 37.5% for erythromycin; at eight weeks, it was 98.5% for the azithromycin group and 50% for the erythromycin group. 50% of patients treated with erythromycin required 8 weeks of treatment as compared to 1.5% of patients treated with azithromycin. The results at 4 weeks of treatment are statistically significant \(t = 2.31, \text{df} = 73, P = 0.0237\). Four-week azithromycin treatment demonstrated statistically significant decreases from baseline in meibomian gland plugging, eyelid margin redness, palpebral conjunctival redness, and ocular discharge \((P < 0.002)\) at day 29, which persisted 4 weeks post-treatment \((P \leq 0.006)\). Patient symptoms of eyelid itching, FBS, ocular dryness, ocular burning/pain, and swollen heavy lids also demonstrated significant improvement from baseline \((P < 0.001)\) for all symptoms and time points except \(P = 0.037\) for ocular dryness. Eyelid margin culture had significant decreases in coagulase-negative staphylococi and Corynebacterium xerosis bacteria. Changes in tear cytokine concentrations were not observed. 12 subjects experienced 19 adverse events. |
| Haque et al³⁷ | 4 weeks of treatment with azithromycin 1.0% ophthalmic solution on eyelid bacterial load, tear cytokines, and symptoms of blepharitis | 26 (4 weeks) | Azithromycin 1.0% ophthalmic solution in the absence of warm compresses or eyelid scrubs for 28 days | |
| Reference | Description |
|-----------|-------------|
| Opitz et al<sup>38</sup> | Azithromycin 1.0% ophthalmic solution for posterior blepharitis  
33 patients completed the study. Azithromycin 1.0% ophthalmic solution twice daily for two days, then once every evening for a total of 30 days. TBUT and Schirmer score increased by 52.7% ($P < 0.0001$) and 24% ($P < 0.05$). Corneal and conjunctival staining was reduced by 83.2% and 67.9% ($P < 0.0001$). Lid margin scores were reduced by 33.9% ($P < 0.0001$). Patient symptom scores improved from 2.73 at baseline to 2.21 at 30 days of treatment ($P < 0.01$). Mean OSDI at baseline was 34.44, at two weeks 14.51, and at 30 days was 13.15 ($P < 0.0001$). Clinical significance was demonstrated in reducing patient signs and symptoms with using topical azithromycin. |
| Luchs J<sup>36</sup> | Topical Azithromycin 1.0% ophthalmic solution in the treatment of posterior blepharitis  
21 patients completed the study. Patients were randomized to receive either azithromycin 1.0% plus warm compresses ($n = 10$), vs compresses alone ($n = 11$). Patients were instructed to apply warm compresses to eye for 5–10 minutes twice daily for 14 days. Azithromycin was instilled twice daily for the first 2 days, then once daily for the next 12 days. |
| Foulks et al<sup>39</sup> | Topical azithromycin for the treatment of meibomian gland dysfunction  
22 subjects completed the study. Subjects with symptomatic MGD were recruited. Subjects used azithromycin 1.0% one drop twice daily for 2 days, then once daily for 4 weeks. |
| Pediatric Cochereau et al<sup>44</sup> | Short duration treatment of azithromycin 1.5% eye drops versus oral azithromycin to treat active trachoma  
670 children  
3 groups: topical azithromycin 1.5% twice daily for 2 days, 3 days or oral azithromycin 20 mg/kg in a single dose  
Cure rate per protocol: 93.0%, 96.3%, and 96.6% in 2-day, 3-day, and oral groups respectively. Azithromycin 1.5% groups were non-inferior to oral treatment. Clinical re-emergence rate: 4.2% No adverse events reported |

(Continued)
Table 1. (Continued)

| Reference                  | Treatment type                                      | No. of pts (duration) | Treatment groups                                                                 | Results                                                                 |
|-----------------------------|-----------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Granet et al45              | Comparison of subjects’ tolerability of moxifloxacin 0.5% vs. azithromycin 1.0% in DuraSite® | 125 adults and children (9 years of age and older) | 3 groups (subjects eyes received different drops depending on group): One drop moxifloxacin HCL 0.5% in one eye and one drop azithromycin 1.0% in DuraSite® in the fellow eye vs. one drop moxifloxacin contralateral Tears Naturale II (placebo) vs. one drop azithromycin and contralateral placebo. | Moxifloxacin was more comfortable ($P < 0.0001$), acceptable ($P < 0.0001$) and had less blurring ($P < 0.0001$) than azithromycin at every time point (immediately following instillation, at 1, 3, 5, and 10 minutes post instillation) for both pediatric and adult populations ($P < 0.02$). 27 adverse events were noted in 19 subjects (6 adult and 13 pediatric) including burning, stinging, irritation, post-nasal drip. Azithromycin had greater bacterial eradication on day 3 as compared to tobramycin ($P < 0.001$). No adverse effects noted |
| Bremond-Gignac et al49     | Azithromycin 1.5% eye drops for purulent bacterial conjunctivitis in the pediatric population | 150 Age 4 to 17       | Azithromycin 1.5% one drop twice daily for 3 days vs. tobramycin 0.3% one drop every 2 hours for 2 days then 4 times daily for 5 days | Azithromycin was more comfortable ($P < 0.0001$), acceptable ($P < 0.0001$) and had less blurring ($P < 0.0001$) than azithromycin at every time point (immediately following instillation, at 1, 3, 5, and 10 minutes post instillation) for both pediatric and adult populations ($P < 0.02$). 27 adverse events were noted in 19 subjects (6 adult and 13 pediatric) including burning, stinging, irritation, post-nasal drip. Azithromycin had greater bacterial eradication on day 3 as compared to tobramycin ($P < 0.001$). No adverse effects noted |

Blepharitis

Blepharitis is one of the most common ocular surface disorders encountered by eye care professionals with one study reporting 37%–47% of patients examined by ophthalmologists and optometrists have blepharitis. Blepharitis is classified by its anatomical location with anterior blepharitis afflicting the lash-baring region of the eyelids and posterior blepharitis, also known as meibomian gland dysfunction (MGD), affecting the meibomian glands (MG). While anterior blepharitis is defined by meibomian gland obstruction and inflammatory mediators released by the meibomian glands, posterior blepharitis is characterized by meibomian gland dysfunction (MGD) and a mixed anterior-posterior blepharitis. Regardless of the anatomical classification, blepharitis is generally chronic in nature with bacterial overgrowth and inflammation that contributes to symptoms.

The multifactorial etiology of blepharitis led to several phase 4 clinical trials to evaluate the effectiveness of azithromycin 1.0%. We found six trials that collectively enrolled nearly 300 patients to study the efficacy of azithromycin 1.0% for the treatment of blepharitis. In the first reported study, a prospective, open-label study involving 150 eyes of 75 subjects diagnosed with chronic mixed anterior blepharitis, patients were treated with either topical azithromycin 1.0% or topical ophthalmic erythromycin. After four weeks of treatment, the clinical resolution was 98.5% for the azithromycin group and 37.5% for the erythromycin group. At eight weeks, it was 98.5% and 50% for azithromycin and erythromycin, respectively. Improvement within one month of treatment was demonstrated for subjects treated with azithromycin 1.0% ophthalmic solution ($P = 0.0237$). A second study looked at subjects with posterior blepharitis. Twenty-one patients were randomized in this open-label study to receive azithromycin 1.0% in DuraSite® plus warm compresses, or warm compresses alone ($P = 0.0237$). Improvement was demonstrated for subjects treated with azithromycin 1.0% ophthalmic solution ($P = 0.0237$).
compresses to each eye for 5–10 minutes twice daily for 14 days. Each eye in the azithromycin group received one drop twice daily for the first two days, then once daily for 12 days. Patients in the azithromycin group demonstrated significant improvements in meibomian gland plugging, quality of meibomian gland secretions, and eyelid redness ($P < 0.001$) at 4 weeks. The warm compressed group failed to show any statistically significant improvement in plugging, secretions or eyelid redness.\textsuperscript{36}

In a third study, twenty-six subjects with moderate to severe blepharitis were evaluated in a multicenter open-label study. Subjects with anterior and posterior blepharitis received azithromycin ophthalmic solution 1.0% in the absence of warm compresses or lid scrubs for 28 days.\textsuperscript{37} After four-weeks of treatment with azithromycin 1.0%, a significant decrease in ocular signs (MG plugging, eyelid margin redness, palpebral conjunctival redness, and ocular discharge) was reported ($P < 0.002$). Ocular symptoms (eyelid itching, foreign body sensation/sandiness/grittiness, ocular dryness, ocular burning, and heavy/swollen eyelids) were also statistically improved ($P < 0.001$). Of note, significant reduction in these signs and symptoms persisted for 4 weeks post-treatment. In the same study, tear collection for cytokine analysis and eyelid margin bacterial cultures pre and post treatment were performed. Eyelid margin cultures demonstrated significant decreases in bacterial load especially for coagulase-negative staphylococci and coryneform bacteria. Interestingly, no changes in tear cytokine concentrations were observed.\textsuperscript{37} This result is contrary to a study performed on the murine model.\textsuperscript{28} According to the authors, the lack of significant change in the measurement cytokine concentrations in tears after topical azithromycin treatment ($P > 0.05$) may have been due to timing of evaluations or reflex tearing that occurred during tear collection. This study suggests that despite no statistical improvement, there was a reduction of inflammation as evident by the significant improvement of hyperemia from baseline which is a hallmark sign of inflammation.\textsuperscript{37}

In a fourth study which was an open label study evaluating patients with meibomian gland dysfunction, 33 patients with were treated with azithromycin 1.0% ophthalmic solution twice daily for two days, then every evening for 28 days.\textsuperscript{38} Both objective and subjective findings improved after treatment. Tear break-up time (TBUT) and Schirmer scores increased ($P < 0.0001$ and $P < 0.05$), corneal and conjunctival staining decreased ($P < 0.0001$), and lid margin scores reduced after treatment ($P < 0.0001$). Patient symptoms improved from 2.73 at baseline to 2.21 after 30 days of treatment ($P < 0.01$), and the Ocular Surface Disease Index (OSDI) improved by 57.9% at 2 weeks and 61.8% from baseline at 4 weeks demonstrating azithromycin 1.0% is an effective treatment for patients with posterior blepharitis.\textsuperscript{38}

A fifth study evaluated the clinical signs and symptoms of meibomian gland dysfunction pre and post treatment with azithromycin 1.0% after 4 weeks. It also evaluated the meibomian gland lipids using spectroscopy.\textsuperscript{39} The results of the 17 patients that completed the 4 week study showed statistical improvement of symptoms ($P < 0.001$) and all eyelid signs measured, including number of obstructed meibomian glands, the amount of lid margin erythema, the ease of meibomian gland expression, and the character of the meibomian gland secretions ($P < 0.001$).\textsuperscript{39} Tear break up time was also statistically improved ($P < 0.001$) as well as improvements in phase transition of the meibomian gland lipids by lowering the transition temperature thus allowing for better mobility and ease of expression for the meibomian gland secretions.\textsuperscript{39}

Another study involving adult subjects over the age of nineteen (n = 122) were enrolled in a multicenter, randomized study to compare the clinical efficacy of 0.3%/0.5% tobramycin/dexamethasone (Tobradex ST\textsuperscript{®}, Alcon Pharmaceuticals) ophthalmic suspension compared to azithromycin 1.0% in Durasite\textsuperscript{®} for the treatment of blepharitis/blepharoconjunctivitis.\textsuperscript{40} Patients were randomized to receive one drop of Tobradex ST\textsuperscript{®} four times daily for 14 days or one drop of AzaSite\textsuperscript{®} twice daily for 2 days, then once daily for 12 days. The study looked at global scores of lid margin redness, bulbar and palpebral conjunctival redness, ocular discharge, itching, grittiness, and lid swelling at days 1, 8 and 15. Of the patients enrolled, 96.7% completed the study. Overall, a significantly lower mean global score for ocular signs and symptoms ($P = 0.0002$) was found in subjects treated with Tobradex ST\textsuperscript{®} compared to those treated with azithromycin at day 8. No serious adverse events were reported in either group.\textsuperscript{40}
Additionally, two simultaneous, Phase II, randomized, prospective, multi-center studies evaluated the effect of topical azithromycin 1% in DuraSite® on anterior blepharitis (clinicaltrials.gov NCT00894530 and NCT00892970). One trial had a two-week treatment period, the other trial a four-week treatment period. In the four-week trial, the signs and symptoms of blepharitis at various time points improved (P ≤ 0.05), but statistical significance was not achieved for the primary endpoint of mean lid margin hyperemia in the control group compared to the treatment group with AzaSite. In the two-week trial, there was no statistically significant improvement of the primary endpoint of lid debris for AzaSite treated group. In both trials, the AzaSite treatment group and the vehicle treatment group showed statistically significant improvements relative to baseline for all measured signs and symptoms of blepharitis.

Collectively, the results of both published and unpublished studies of AzaSite for the treatment of blepharitis suggest significant benefit in the treatment of either posterior blepharitis or mixed anterior-posterior blepharitis while the Phase II clinical trials of anterior blepharitis did not meet primary endpoints.

Contact lens and dry eye
A recent study evaluated the safety and efficacy of azithromycin ophthalmic solution 1% in patients with contact lens-related dry eye (CLDE). This 4-week, single-center, open-label clinical trial enrolled 50 patients diagnosed with CLED using the Contact Lens Dry Eye Questionaire (CLDEQ). Patients were randomized to receive azithromycin 1% ophthalmic solution twice a day then once a day for 29 days or to receive Visine for Contacts 4 times daily for one month. Results showed a statistically significant increase in mean comfortable contact lens wear time from baseline for the subjects treated with azithromycin ophthalmic solution as compared with the subjects treated with rewetting drops at week 4 (P = 0.004; primary endpoint). This was a similar effect seen at weeks 2 and 3. The improvement in the mean comfortable wear time for the patients in the azithromycin treatment group exceeded 2 hours throughout the treatment period (weeks 1–4). No significant differences were observed between the groups for total wear time, low contrast visual acuity, or tear osmolarity. Subject-rated ocular dryness (evening time assessments) was significantly improved from baseline in the subjects treated with azithromycin ophthalmic solution as compared with those treated with rewetting drops at weeks 2 and 3 endpoints (P = 0.015 for each week). Additionally, a statistical difference was observed in favor of the azithromycin treatment group at week 2 for the subjects reclassifying as non-dry eye as determined by the CLDEQ (P = 0.05).

Trachoma
Trachoma, the leading cause of infectious blindness worldwide, is a chronic keratoconjunctivitis caused by Chlamydiae trachomatis. Oral azithromycin has been found to be an effective treatment for trachoma, but systemic side effects of the oral formulation may limit its use. The high tissue concentration, long duration of action, and simple dosing regimen, makes topical azithromycin an ideal treatment option for trachoma. Several studies have researched the safety and efficacy of topical azithromycin 1.5% for the treatment of trachoma. Epidemiology studies of trachoma were performed on the entire population of the Kolofata Health District of Cameroon. The treatment included one drop of azithromycin 1.5% in both eyes in the morning and in the evening for three consecutive days. Before treatment, the prevalence of trachoma was estimated to be 31.5%. One year after mass treatment, the prevalence was reduced by nearly 80% to 6.3% and one year after the second year of treatment, the prevalence dropped to 3.1%, a reduction of 90%. Only minor side effects were noted throughout treatment such as blurred vision and a burning sensation. This study demonstrates that topical azithromycin may be as effective as oral azithromycin, which may be especially beneficial for the treatment of trachoma in young children and pregnant women.

Another randomized, controlled, double masked study of trachoma included over 670 children aged 1 to 10 years old from Guinea Conakry and Pakistan. This study compared the safety and efficacy of azithromycin 1.5% eye drops versus oral azithromycin for the treatment of active trachoma. Individuals were randomized to receive either azithromycin 1.5% drops twice daily for two or three days, or a single dose of oral azithromycin (20 mg/kg). The results of this study found that azithromycin 1.5% is as effective as
a single dose of oral azithromycin in the treatment of active trachoma.44

Azithromycin 1.5% was used in these studies for the treatment of trachoma. Additional studies using the 1% formulation should be performed. Based on the 1.5% studies, topical azithromycin has the potential to be a potent alternative to the oral formulation of azithromycin for this potentially blinding disease.

Safety and Tolerability
The first published report that evaluated the safety and efficacy of azithromycin 1.0% in the treatment of active bacterial conjunctivitis was a prospective, multicenter, randomized phase 3 clinical trial where subjects were randomized to receive 1.0% azithromycin in DuraSite® or 0.03% tobramycin.31 Both medications were well tolerated among the subjects who completed the trial (n = 710). The adverse events in this study were reported after using a dosing schedule of twice daily dosing for 2 days followed by once daily dosing for 3 more days (5 day total treatment). The adverse events included eye irritation (1.9%), conjunctival hyperemia (1.1%), and worsening of the conjunctivitis (1.1%).31

A separate published study evaluated tolerability of a single dose of azithromycin 1.0% in DuraSite® to moxifloxacin 0.5% at different time points.45 The study design was subject-masked, randomized, active and placebo-controlled. Of the 125 normal, healthy subjects who received either moxifloxacin 0.5%, azithromycin 1.0% in DuraSite® or Tears Natural II®, the azithromycin group had a higher a rate of adverse events (17.3%) compared to the moxifloxicin group (1%).45 The authors concluded that the DuraSite® vehicle in AzaSite® increased contact time of both azithromycin and the preservative, bezalkonium chloride (BAK).

We further reviewed all published human studies that used azithromycin 1.0% twice daily for 2 days followed by once daily dosing for an additional 3–5 days as part of the study protocol (total treatment of 5–7 days). The most common side effects of these studies reviewed included ocular burning or stinging 1.5%, foreign body sensation on instillation 1.4%, headache 1.2%, conjunctival edema <1.1%, blurred vision 1.8%, worsening of condition <1.5%.31–33 In other human studies that required treatment protocols longer than 14 days,35–39 the reported side effects included eye pain 15%, blurred vision 5%–15%, eye irritation 2%–5%, eye pruritus 4%–8%, eye discharge 4%, and eye burning 4%. Based on these results, the rate for adverse events was higher in treatment protocols that were longer than 7 days, although none were considered serious. The length of time of treatment seemed to have an effect on the occurrence rate with the exception of the study by Granet, et al which showed a single dose of azithromycin 1.0% in DuraSite® caused ocular adverse events in 17.3% after a single dose.45

Although numerous published clinical trials report on the safety and efficacy of topical azithromycin, two unpublished trials listed in the Cochrane Register of Controlled Trials evaluated the efficacy and tolerability of the drug compared to vehicle. The first study by Heller, et al, included 685 patients with clinically evident bacterial conjunctivitis.46 This study compared the adverse events rate of 1% azithromycin in DuraSite® to that of the vehicle, DuraSite®. Results showed that at least one adverse event occurred in 12% of subjects in both azithromycin group and the placebo group.46 The second trial enrolled patients with bacterial conjunctivitis, but this study compared the clinical resolution of bacterial conjunctivitis of patient treated with 1% azithromycin to patients treated with the vehicle, DuraSite®.47 Results demonstrated bacterial irradiation was significantly better in the eyes treated with azithromycin compared to the vehicle group.47

Patient Considerations
One of the distinct advantages that AzaSite® may have over other treatment options for ocular surface diseases such as bacterial conjunctivitis is the limited number of drops necessary to achieve the desired therapeutic effect. The “on-label” treatment protocol for bacterial conjunctivitis with AzaSite® is twice daily for 2 days, then once daily for an additional 5 days for a total of 9 drops per affected eye.14 It has been well documented that patient non-adherence to antibiotics can contribute to bacterial resistance. Further, complicated multiple dosing regimens in both the adult and pediatric patients can also contribute to non-adherence. Several of the clinical studies that we reviewed, included patients of pediatric ages. We found seven clinical trials, summarized in Table 1, which
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collectively enrolled both pediatric and adult patients to study the efficacy of azithromycin for the treatment of bacterial conjunctivitis and blepharitis. Given the susceptibility of AzaSite® to *H. influenza*, *S. pneumonia*, and *Moraxella catarrhalsi* which are the most common pathogens in pediatric bacterial conjunctivitis, Azasite® is especially useful in this population.

Topical antibiotics have become the standard of care during the pre and post-operative care of intra-operative ophthalmic surgeries to prevent and treat microbial infections such as endophthalmitis. Azasite® has been shown to have high conjunctival tissue concentrations which could be helpful to prevent microbial infections, but the low aqueous humor concentrations make it less than ideal to treat endophthalmitis. One study evaluated the safety of DuraSite® if introduced into the anterior chamber. These results lead the authors to conclude that DuraSite® antibiotics could cause both acute glaucoma and anterior chamber toxicity. The authors went on to suggest suturing of corneal incisions to ensure that DuraSite® is not introduced into the anterior chamber. Another study compared toxicity of intraocular azithromycin 1.0% with and without DuraSite® in rabbit eyes. One eye in each rabbit received azithromycin with the delivery system (study) and the other eye received azithromycin without the delivery system (control). The results indicated that intraocular pressure, corneal thickness and inflammatory signs were consistently higher in the study eye as compared to the control eye. Their results demonstrated an increase in intraocular pressure and corneal thickness resulting from edema and inflammation as the drug-delivery system gained access to the anterior chamber.

Although azithromycin 1.0% in DuraSite® may not have a practical role for intraoperative surgery yet, one animal based study looked at its potential for corneal based refractive surgery. In that study, hens were divided into groups regarding surgical procedure: photorefractive keratectomy (PRK), laser-assisted in situ keratomileusis (LASIK), or no surgery. Groups were treated with T1225 oil based azithromycin eye drops bid 3 days prior to and 3 days post-surgery, saline drops, or no treatment. None of the azithromycin treated eyes had infections post-surgery and clinical signs were reduced with this group. T1225 azithromycin eye drops were well tolerated in both unmanipulated corneas and those treated with refractive surgery, demonstrating that T1225 is an effective antibiotic after refractive surgical treatment. Although studies have not been done on human subjects, this study suggests that with more investigation, azithromycin may have a future role in the treatment of surgical care.

Conclusions

Bacterial conjunctivitis and blepharitis are common conditions that are routinely encountered by the eye-care practitioner. The results of this literature review demonstrate that azithromycin 1.0% in DuraSite® is an effective and safe treatment for these ocular conditions in both the pediatric and adult populations. Additionally, contact lens related dryness improved after treatment with 1% azithromycin and the 1.5% formulation was effective for the treatment of *trachoma*. In addition to its anti-microbial and anti-inflammatory effects, AzaSite® in DuraSite® has been found to maintain prolonged drug residence time, have a less frequent dosing regimen, thus increasing patient compliance. This is of importance as AzaSite® continues to be studied for the treatment of ocular conditions beyond its clinical indication.

Author Contributions

Conceived and designed the experiments: DLO, JSH. Analysed the data: DLO, JSH. Wrote the first draft of the manuscript: DLO, JSH. Contributed to the writing of the manuscript: DLO, JSH. Agree with manuscript results and conclusions: DLO, JSH. Jointly developed the structure and arguments for the paper: DLO, JSH. Made critical revisions and approved final version: DLO, JSH. All authors reviewed and approved of the final manuscript.

Competing Interests

Dominick L. Opitz was a prior educational speaker for Inspire Pharmaceuticals. Prior to May 2011, Dominick L. Opitz held stock in Inspire.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributor-ship, conflicts of interest, privacy and confidentiality...
and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

References
1. Retsema J, Girard A, Schelkly W, et al. Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered macroline with improved potency against gram-negative organisms. *Antimicrob Agents Chemother.* 1987;31:1393–47.
2. Gladue RP, Snider ME. Intracellular accumulation of azithromycin by cultured human fibroblasts. *Antimicrob Agents Chemother.* 1999;34:1056–60.
3. Gladue RP, Bright GM, Isaacson RE, Newborg MF. In vitro and in vivo uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. *Antimicrob Agents Chemother.* 1989;33:785–93.
4. Rapp RP. Pharmacokinetics and pharmacodynamics of intravenous and oral azithromycin: enhanced tissue activity and minimal drug interactions. *Ann Pharmacother.* 1989;23:531–5.
5. Jain R, Danziger LH. The macroline antibiotics: a pharmacokinetic and pharmacodynamic overview. *Curr Pharm Des.* 2004;10:3045–53.
6. West SK. Azithromycin for control of trachoma. *Commun Eye Health.* 1999;12:55–6.
7. Solomon AW, Holland MJ, Alexander NDE, et al. Mass treatment with single-dose azithromycin for trachoma. *N Engl J Med.* 2004;351:1662–71.
8. Karcigolu ZA, Ahmed WS, Raines D, El-Yazigi A. Pharmacokinetics of azithromycin rabbit lacrimal glands and conjunctiva. *Ophthamol Res.* 1999;31(1):47–52.
9. O’Day DM, Head FS, Foulds G, Robinson RD, Williams TE, Ferraina RA. Ocular pharmacokinetics of orally administered azithromycin in rabbits. *J Ocul Pharmacol.* 1994;10(4):633–41.
10. Tabbara KF, Al-Kharashi SA, Al-Man souri SM, et al. Ocular levels of azithromycin. *Arch Ophthamal.* 1998;116(12):1625–8.
11. Janaro A, Ialenti A, Maffia P, et al. Anti-inflammatory activity of macrolide antibiotics. *J Pharmacol Exp Ther.* 2000;292:156–63.
12. Scaglione F, Rossioni G. Comparative anti-inflammatory effects of toxi thromycin, azithromycin and clarithromycin. *J Antimicrob Chemother.* 1998;41:47–50.
13. Agahi ZH, Kode A, Saslow JG, et al. Azithromycin suppresses activation of nuclear factor-kappa B and synthesis of pro-inflammatory cytokines in tracheal aspirate cells from premature infants. *Pediatr Res.* Oct 2007;62(4):483–8.
14. Azasite [Package Insert]. Durham, NC: Inspire Pharmaceuticals; 2008.
15. Friedlaender MH, Protzko E. Clinical development of 1% azithromycin in DuraSite®, a topical azalide anti-infective for ocular surface therapy. *Clin Ophthalmol.* 2007;1(1):3–10.
16. Kerce M, Bogotaj M, Mugerle B, Gäsperlin M, Mrhar A. Mucoadhesion on pig vesical mucosa: influence of polycarbophil/calcium interactions. *Int J Pharm.* 2002;241:135–43.
17. Bowman LM, Si E, Pang J, Archibald R, Friedlaender M. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133–9.
18. Akpek EK, Vithitorn J, Verhoeven RS, et al. Ocular surface distribution and pharmacokinetics of a novel ocular 1% azithromycin formulation. *J Ocul Pharmacol Ther.* 2009;25(5):433–9.
19. Stewart WC, Crean CS, Zink RC, Brubaker K, Haque R, Hwang DG. Pharmacokinetics of azithromycin and moxifloxacin in human conjunctiva and aqueous humor during and after the approved dosing regimens. *Am J Ophthalmol.* 2010;150:744–51.
20. Torkildsen O, O’Brien TP. Conjunctival tissue pharmacokinetic properties of topical azithromycin 1% and moxifloxacin 0.5% ophthalmic solutions: a single-dose, randomized, open-label, active-controlled trial in healthy adult volunteers. *Clin Ther.* 2008;30(11):2005–14.
21. Chiambaretta F, Garraffo R, Elena PP, et al. Tear concentrations of azithromycin following topical administration of a single dose of azithromycin 0.5%, 1.0%, and 1.5% eyedrops (T1225) in healthy volunteers. *Eur J Ophthalmol.* 2008;18(1):13–20.
22. Carbon C. Pharmacodynamics of macrolides, azalides and streptogramins: effect on extracellular pathogens. *Clin Infect Dis.* 1998;27:28–32.
23. Drofman MS, Wagner RS, Jamison T, Bell B, Stroma DW. The pharmacodynamics properties of azithromycin in a kinetic-of-kill model and implications for bacterial conjunctivitis treatment. *Adv Ther.* 2008;25(3):208–17.
24. Elder MJ, Stapleton F, Evans E, et al. Biofilm-related infections in ophthalmology. *Eye (Lond).* 1999;9(Pt 1):102–9.
25. Zegans ME, Becker HI, Budzik J, et al. The role of bacterial biofilms in ocular infections. *DNA Cell Biol.* 2002;21:415–20.
26. Aslam S. Effect of antibacterials on biofilms. *Curr Med Res Opin.* 2008;24(3):208–17.
27. Sadrai Z, Hajrasoulia AR, Chauhan S, Saban DR, Dastjerdi MH, Dana R. Effect of topical azithromycin on corneal innate immune response. *Invest Ophthalmol Vis Sci.* 2011;52(5):2525–31.
28. Li DQ, Zhou N, Zhang L, Ma P, Pflugfelder SC. Azithromycin Suppresses Zymosan-induced production of Pro-inflammatory Mediators by Human Corneal Epithelial Cells. *Invest Ophthalmol Vis Sci.* 2010;51:5623–9.
29. Sheikh A, Hurwitz B. Topical antibiotics for acute bacterial conjunctivitis: a systematic review. *Br J Ophthalmol.* 2001;85:473–7.
30. Protzko E, Bowman L, Abelson M, et al. Phase 3 safety comparisons for 1.0% azithromycin in polymeric mucoadhesive eye drops versus 0.3% tobramycin eye drops for bacterial conjunctivitis. *Invest Ophthalmol Vis Sci.* 2007;48(8):3425–9.
31. Abelson MB, Heller W, Shapiro AM, et al. Clinical cure of bacterial conjunctivitis with Azithromycin 1%; vehicle-controlled, double-masked clinical trial. *Am J Ophthalmol.* 2008;145:959–65.
32. Abelson M, Protzko E, Shapiro A, et al. A randomized trial assessing the clinical efficacy and microbial eradication of 1% azithromycin ophthalmic solution vs tobramycin in adult and pediatric subjects with bacterial conjunctivitis. *Clin Ophthalmol.* 2007;1(2):177–82.
33. Lenp MA, Nichols KK. Blepharitis in the United States 2009: a survey-based perspective on prevalence and treatment. *Ocul Surf.* 2009;7 Suppl 2:S1–14.
34. John T. Use of azithromycin ophthalmic solution in the treatment of chronic mixed anterior blepharitis. *Ann Ophthalmol.* 2008;40(2):68–74.
35. Luchs J. Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of postoperative blepharitis. *Adv Ther.* 2008;25(9):858–70.
36. Haque RM, Torkildsen GL, Brubaker K, et al. Multicenter open-label study evaluating the efficacy of azithromycin ophthalmic solution 1% on the signs and symptoms of subjects with blepharitis. *Cornea.* 2010;29:871–7.
37. Opitz DL, Tyler, KF. Efficacy of azithromycin ophthalmic solution for treatment of ocular surface disease from posterior blepharitis. *Clin Exp Optom.* Mar 2011;94(2):200–6.
38. Foukis GN, Borchman D, Yappert M, et al. Topical azithromycin therapy for meibomian gland dysfunction: clinical response and lipid alterations. *Cornea.* 2010;29:781–8.
39. Torkildsen GL, Cockrum P, Meier E, et al. Evaluation of clinical efficacy and safety of tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% compared to azithromycin ophthalmic solution 1% in the treatment of moderate to severe acute blepharitis/blepharocconjunctivitis. *Curr Med Res Opin.* 2011;27(1):171–8.
41. Utine CA. Update and critical appraisal of the use of topical azithromycin ophthalmic 1% (Azasite®) solution in the treatment of ocular infections. Clin Ophthalmol. 2011;5:801–9.

42. Nichols JJ, Bickle KM, Zink RC, Schieve MD, Haque RM, Nichols KK. Safety and efficacy of topical azithromycin ophthalmic solution 1.0% in the treatment of contact lens-related dry eye. Eye Contact Lens. Feb 2012. DOI: 10.1097/ICL.0b013e31823f229 (Epub ahead of print).

43. Amza A, Goldschmidt P, et al. Elimination of active trachoma after two topical mass treatments with azithromycin 1.5% eye drops. PLoS Negl Trop Dis. 2010;4(11):e895.

44. Cochereau I, Goldschmidt AG, Afghani T, et al. Efficacy and safety of short duration azithromycin eye drops versus azithromycin single oral dose for the treatment of trachoma in children: a randomized, controlled, double-masked clinical trial. Br J Ophthalmol. 2007;91:667–72.

45. Granet D, Lichtenstein SJ, Onofrey B, Katz JA. As assessment of the tolerability of moxifloxacin 0.5% compared to azithromycin 1.0% in DuraSite. Clin Ophthalmol. 2007;1(4):519–25.

46. Heller W, Abelson M, Group TAS. Safety and tolerability of azithromycin 1% eye drops as anti-infective therapy for bacteria conjunctivitis. Unpublished study for the Cochrane Register of Controlled Trials (CENTRAL). Study IDCN00634521.

47. Abelson M, Heller W. Efficacy of azithromycin 1% eye drops vs vehicle as first line therapy for bacterial conjunctivitis. Unpublished study the Cochrane Register of Controlled Trials (CENTRAL). 2006;IDCN00634804.

48. Denis F, Chaumeil C, Goldschmidt P, et al. Microbiologic efficacy of 3-day treatment with azithromycin 1.5% eyedrops for purulent bacterial conjunctivitis. Eur J Ophthalmol. 2008;18(6):858–68.

49. Bremond-Gignac D, Mariani-Kurkdjian P, Beresniak A, et al. Efficacy and safety of azithromycin 1.5% eye drops for purulent bacterial conjunctivitis in pediatric patients. Pediatr Infect Dis J. 2010;29(3):222–6.

50. Lichtenstein SJ, Granet DB. Fluoroquinolones compared to 1% azithromycin in DuraSite® for bacterial conjunctivitis. Clin Ophthalmol. 2008;2(1):241–2.

51. Ness PJ, Mamalis N, Werner L, et al. An anterior chamber toxicity study evaluating besivance, azasite, and ciprofloxacin. Am J Ophthalmol. 2010;150:498–504.

52. Goecks T, Werner L, Mamalsi N, et al. Toxicity comparison of intraocular azithromycin with and without a bioadhesive delivery system in rabbit eyes. J Cataract Refract Surg. 2011;38:137–45.

53. Merayo-Lloves J, Blanco-Mezquita T, Ibares-Frias L, et al. Efficacy and safety of short-duration topical treatment with azithromycin oil-based eyedrops in an experimental model of corneal refractive surgery. Eur J Ophthalmol. 2010;20(6):979–88.

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