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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

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Objective: The study was designed to evaluate the efficacy of an ophthalmic formulation of 1% azithromycin in DuraSite® (AzaSite™, InSite Vision, Alameda CA, USA) and demonstrate equivalence with 0.3% tobramycin ophthalmic solution, USP, for the treatment of bacterial conjunctivitis as defined by the resolution of clinical signs and the eradication of pathogens.

Design: Prospective, randomized, active-controlled, double-masked, phase 3 trial conducted at 47 US sites between 6 August 2004 and 6 October 2005. Participants: Subjects aged 1 year or older with diagnosis of acute bacterial conjunctivitis.

Methods: Bacteriologically confirmed participants received either 1% azithromycin in Dura-Site (n = 159) or tobramycin (n = 157). Masked study medications were dosed 4 times a day for 5 days. Participants in the 1% azithromycin in DuraSite group were dosed twice a day with active drug on days 1 and 2 and once daily on days 3 through 5. The other doses were vehicle. Clinical signs and bacterial cultures were evaluated at visit 3 (day 6 + 1).

Results: Clinical resolution was observed in 79.9% of participants in the 1% azithromycin in DuraSite group, as compared with 78.3% of those in the tobramycin group (95% CI: -7.4-10.5). Bacterial eradication was 88.1% in the 1% azithromycin in DuraSite group vs 94.3% in the tobramycin group (95% CI: -12.4-0.0). Analyses of resistance confirmed that 1% azithromycin in DuraSite eradicated *Staphylococci* and *Streptococci* strains that are commonly resistant to azithromycin, erythromycin, and fluoroquinolones.

Conclusions: The efficacy of 1% azithromycin in DuraSite and tobramycin are equivalent; however, this formulation of azithromycin also permits effective dosing intervals of twice a day on days 1 and 2 followed by once daily on the last 3 days of therapy, for a total of 65% fewer doses. In vitro, the killing spectrum of 1% azithromycin in DuraSite appears to be enhanced relative to 1% azithromycin without DuraSite.

Keywords: azithromycin, bacterial conjunctivitis, tobramycin, ophthalmic solution

Introduction

Acute bacterial conjunctivitis is an infective condition in which the eyes become red and inflamed. The pathogens vary, but the majority of bacterial conjunctivitis infections are caused by *Haemophilus influenzae*, *Staphylococcus aureus*, or *Streptococcus pneumoniae* (Seal 1982). Common in children, these infections are often self-limiting and usually resolve in 8–10 days. Untreated bacterial conjunctivitis in contact lens wearers, however, may have very serious consequences because of the potential for corneal ulcer development. In addition, epidemics of atypical bacterial conjunctivitis have occurred on college campuses (Martin et al 2003), and the threat of contagion among children in the US is perceived as sufficiently significant that infected children

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are not allowed to return to school or daycare until they have received adequate therapeutic intervention (American Academy of Pediatrics 2003).

Effective ocular antibiotics with shorter and more simplified dosing regimens could improve treatment compliance, thereby improving treatment efficacy and reducing a contagion's spread (Alvarez-Elcoro and Enzler 1999; Kardas 2002). To that end, a new topical ocular solution of 1% azithromycin was formulated with DuraSite® (AzaSite™, InSite Vision, Alameda, CA), an ocular delivery system. This delivery vehicle stabilizes azithromycin in an aqueous mucoadhesive matrix and permits an increase in the concentration of azithromycin in ocular tissue sufficient to kill bacteria commonly associated with conjunctivitis.

The efficacy of 1% azithromycin in DuraSite was compared with that of tobramycin 0.3% eye drops in a therapeutic regimen of 5 days. Tobramycin was chosen as the comparator owing to its well-known efficacy; low side effects profile; availability in the US; and formulation as an eye drop, which allowed for easy masking.

Methods

The primary objective of the study was the clinical resolution of the signs and symptoms of infective bacterial conjunctivitis. Resolution was defined as a clinical severity rating of 0 for each of 3 clinical observations: ocular discharge, bulbar injection, and palpebral injection. The secondary objective was bacterial eradication, which was defined by the absence in culture of the original infecting bacteria. Clinical resolution and bacterial eradication were both evaluated at the third test-of-cure visit (day 6 or 7).

Subjects were deemed eligible if they were 1 year or older, with no evidence of debilitating disease. Clinical signs necessary for inclusion in the trial included purulent conjunctival discharge and conjunctival or palpebral injection of no more than 3 days' duration. Individuals were required to exhibit a minimum score of grade 1 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) for purulent conjunctival discharge and a minimum score of grade 1 (0 = normal, 1 = mild, 2 = moderate, 3 = severe) for either bulbar or palpebral injection in the same eye. Investigators scored the extent of injection by referring to standardized photographs (Ophthalmic Research Associates, North Andover, MA). At study entry, eligible participants had a best corrected visual acuity of 20/100 or better, and were required to discontinue contact lens wear, and, if female, and of child-bearing potential, to test negative for pregnancy. Potential participants who had

used topical ophthalmic solutions or anti-inflammatory agents prior to study entry were excluded.

Participants were randomized to receive either 1% azithromycin in DuraSite or 0.3% tobramycin. Conjunctival cultures were obtained from these intent-to-treat participants at presentation on day 1. The efficacy analysis was performed on the per-protocol sample. Those eligible for efficacy analysis had positive results for bacterial cultures, no major protocol violations, and completed at least 1 post-dose follow-up. A positive culture was determined by previously defined minimum threshold bacterial counts (Cagle et al 1981). A sample size of 155 participants per treatment arm was deemed sufficient for the comparison of equivalence based on a power of 0.90, and $\alpha = 0.05$ (2-sided 95% intervals).

Participants were directed to instill the study medication into the worse affected eye 4 times a day. Many patients were infected in both eyes (70.6%, 223/316); in these cases both eyes were treated. There was no significant difference ($p = 0.20$) between treatment groups in the proportion of participants who received bilateral treatment. If both eyes were infected the eye with the worse signs was used for analysis.

The study design is shown in Figure 1.

Results

Randomization

Of the 743 eligible participants who were randomized, 710 (95.6%) completed the trial. Positive ocular bacterial cultures were confirmed in 316 (42.5%) participants. Of the eligible population, 33 participants were terminated from the study before completion. Of these, 17 were dropped as a result of adverse events and the remaining 16 were dropped because of protocol violations, withdrawn consent, losses to follow up, or lack of efficacy. The major protocol violation in this study was failure to return for one of the two follow-up visits.

Demographics

The median age of participants in the per-protocol population was 20.4 ± 21.5 years (range 1–83). The percent of participants 11 years old or younger was 53.8%. The only demographic difference between treatment groups that was statistically significant was a difference in mean age of approximately 5 years ($p = 0.045$) (Table 1).

Baseline signs and symptoms

More than 50% of participants were classified with clinical signs and symptoms of moderate severity at the baseline visit on day 1. Overall 10% to 13% presented with severe clinical

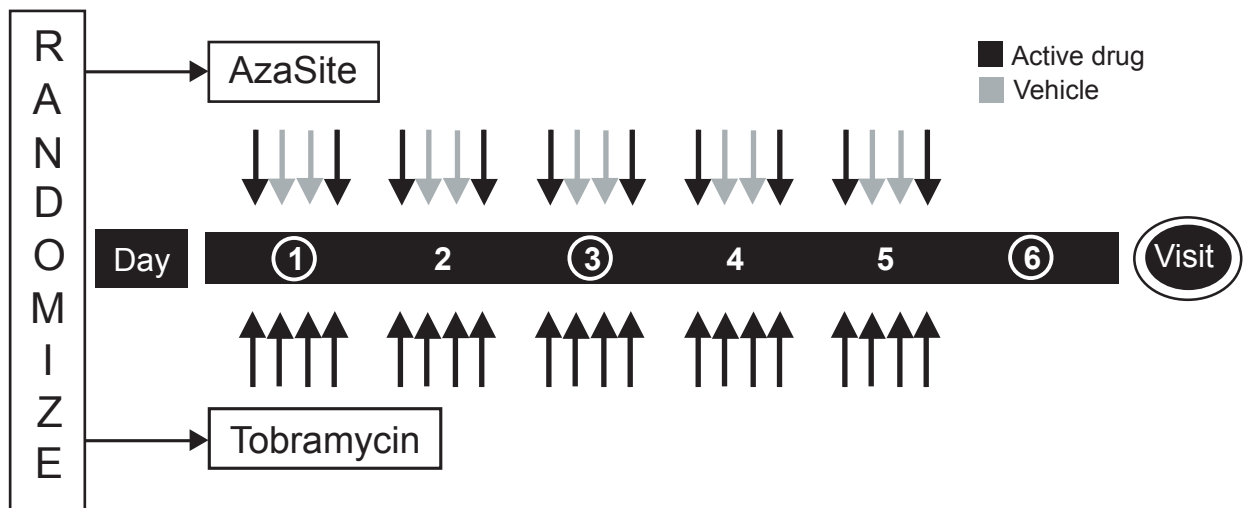


Figure 1 Study design and dosing scheme. Masked study medications were dosed 4 times per day for 5 days. Participants in the azithromycin group only received active study medication twice a day on days 1 and 2 and once daily on days 3 through 5. Study visit evaluations included: clinical assessment, best corrected visual acuity, biomicroscopy, ophthalmoscopy (days 1 and 6 only), and cultures from infected eye(s).

signs (Table 2). There were no significant differences between the treatment groups in the severity of signs and symptoms.

Clinical resolution

The therapy was rated as either a success or failure based on the complete resolution of clinical symptoms (Table 3). Treatment with 1% azithromycin in DuraSite achieved clinical resolution in 79.9% (127/159) of participants; treatment with tobramycin achieved clinical resolution in 78.3% (123/157) of participants. The difference in clinical resolution between the two treatment groups was not statistically significant ($p = 0.783$).

Investigator ratings of clinical outcomes

Clinical outcomes were based on the investigator severity ratings of ocular discharge and injection. At day 3, 93.9% of infections that were treated with 1% azithromycin in DuraSite were resolved or improved. There were no statistically significant differences ($p = 0.949$) between the treatment groups. However, equivalence with tobramycin was obtained with 65% fewer drops of 1% azithromycin in DuraSite (Table 4).

Bacterial eradication

Cultures of the ocular swabs performed at baseline revealed that the distribution and frequency of causative pathogens in the two treatment groups was similar. The most prevalent bacteria cultured from participants in the 1% azithromycin in DuraSite treatment group were *H. influenzae* (42.8%, $n = 68$),

S. pneumoniae (39.6%, $n = 63$), *S. aureus* (12.6%, $n = 20$), and *Staphylococcus epidermidis* (3.1%, $n = 5$). The frequencies of other pathogens were lower.

Treatment with 1% azithromycin in DuraSite achieved bacterial eradication in 88.1% of participants (140/159). Comparably, treatment with tobramycin achieved bacterial eradication in 94.3% (148/157). The difference between treatment groups was not statistically significant ($p = 0.073$; Table 5).

Supplementary evaluations of eradication with respect to gram stain were also performed. At visit 3, eradication of gram-positive *S. aureus*, and *S. pneumoniae*, was 82.4% and 87.5%, respectively. The rate of eradication of gram-negative *H. influenzae* was 93%. There were no statistically significant differences between treatment groups in terms of efficacy against the most common gram-positive and gram-negative pathogens of bacterial conjunctivitis.

In vitro sensitivity testing

The resistance patterns in the pathogens isolated from the participants were evaluated in vitro using systemic breakpoints defined by the Clinical Laboratory and Standards Institute (CLSI). Azithromycin in DuraSite effectively eradicated several *Staphylococci* and *Streptococci* strains that were observed to be resistant to azithromycin, erythromycin, levofloxacin, gatifloxacin, moxifloxacin, and oxacillin (Table 6).

The azithromycin in DuraSite formulation eradicated 2 of 4 isolates (50.0%) of azithromycin-resistant *S. aureus*. Nine of 15 isolates (60.0%) of resistant gram-negative *S. pneumoniae*

Table 1 Study participant demographics in the per-protocol population

	1% azithromycin			p value
	in DuraSite (n = 159)	0.3% tobramycin (n = 157)	Total (n = 316)	
Age				
Mean \pm SD	17.9 \pm 20.23	22.8 \pm 20.23	20.4 \pm 20.23	0.045 ^a
Median (range, y)	8 (1–81)	12 (1–83)	9 (1–83)	
Pediatric (1–11 y)	93 (58.5%)	77 (49.0%)	170 (53.8%)	0.114
Non-pediatric (>12 y)	66 (49.1%)	80 (42.7%)	146 (45.9%)	
Non-geriatric (<65 y)	153 (96.2%)	147 (93.6%)	300 (94.9%)	0.317
Geriatric (>65 y)	6 (3.8%)	10 (6.4%)	16 (5.1%)	
Sex				
Male	78 (49.1%)	67 (47.2%)	145 (45.9%)	0.261
Female	81 (50.9%)	90 (57.3%)	171 (54.1%)	
Race				
White	113 (71.1%)	100 (63.7%)	213 (67.4%)	0.429
Black	10 (6.3%)	15 (9.6%)	25 (7.9%)	
Asian or Pacific Islander	3 (1.9%)	4 (2.5%)	7 (2.2%)	
Hispanic	29 (18.2%)	37 (23.6%)	66 (20.9%)	
Native American or Alaskan	1 (0.6%)	0	1 (0.3%)	
Other	3 (1.9%)	1 (0.6%)	4 (1.3%)	
Eye color				
Brown	82 (51.6%)	78 (49.7%)	160 (50.6%)	0.202
Blue	50 (31.4%)	48 (30.6%)	98 (31.0%)	
Green	12 (7.5%)	5 (3.2%)	17 (5.4%)	
Hazel	12 (7.5%)	21 (13.4%)	33 (10.4%)	
Other	3 (1.9%)	5 (3.2%)	8 (2.5%)	
Iris color (hue)				
Dark	84 (52.8%)	83 (52.9%)	167 (52.8%)	0.191
Hazel	12 (7.5%)	21 (13.4%)	33 (10.4%)	
Light	63 (39.6%)	53 (33.8%)	116 (36.7%)	

^ap < 0.05; p value from Fisher Exact Test.

were also eradicated. Although the incidence was low, 1% azithromycin in DuraSite eradicated 100% of the other resistant *Staphylococci* and *Streptococci* strains that were cultured in this study (Table 6). A similar pattern of eradication was observed with tobramycin-resistant pathogens.

A few strains of *S. aureus* and *Staphylococcus simulans* were resistant to fluoroquinolones and oxacillin in culture. Azithromycin in DuraSite was able to eradicate half the *S. aureus* and the *S. simulans* isolates that were resistant to the third- and fourth-generation fluoroquinolones. The azithromycin formulation in DuraSite also eradicated the two oxacillin-resistant *Staphylococci* isolates encountered in the study (see Table 6).

By comparison, tobramycin was effective against 83% (5/6) of the oxacillin-resistant *Staphylococci* strains and eradicated 76% (19/25) of the azithromycin-resistant bacterial strains tested.

Discussion and conclusions

The efficacy of a 5-day regimen of topical 1% azithromycin in DuraSite, a new anti-infective eye drop, against infective bacterial conjunctivitis was compared with that of 0.3%

tobramycin ocular solution. Erythromycin, a macrolide, is closely related to azithromycin but azithromycin's pharmacologic profile is improved with respect to bacterial eradication spectrum, higher tissue penetration, and a longer half-life (Neu 1991; Bryskier and Labro 1994).

The formulation of azithromycin in DuraSite forms a stable, mucoadhesive matrix that increases the bioavailability of azithromycin in the eye. The dosing regimen in this clinical trial was twice a day on days 1 and 2 and once daily on days 3 through 5.

As with other ocular anti-infectives, the strategy employed was to deliver higher drug levels earlier in the course of infection when the bacterial burden is likely to be highest. The results indicate that the formulation of 1% azithromycin in DuraSite was just as effective as tobramycin eye drops and demonstrated the potential advantage of requiring 65% fewer drops for a full course of therapy. Likewise with respect to bacterial eradication, there was no difference in the rate of pathogen clearance over the 5-day course of therapy. Coverage of gram-negative and gram-positive pathogens was equally effective. The most commonly used 4th generation fluoroquinolone eye drops, moxifloxacin and

Table 2 Clinical signs and symptoms at baseline

	1% azithromycin in DuraSite (n = 159)	0.3% tobramycin (n = 157)	Total (n = 316)
Ocular discharge			
Absent	0	0	0
Mild	54 (34.0%)	61 (38.9%)	115 (36.4%)
Moderate	83 (52.2%)	82 (52.2%)	165 (52.2%)
Severe	22 (13.8%)	14 (8.9%)	36 (11.4%)
Bulbar conjunctival injection			
Normal	1 (0.6%)	1 (0.6%)	2 (0.6%)
Mild	54 (34.0%)	43 (27.4%)	97 (30.7%)
Moderate	89 (56.0%)	95 (60.5%)	184 (58.2%)
Severe	15 (9.4)	18 (11.5%)	33 (10.4%)
Palpebral conjunctival injection			
Normal	3 (1.9%)	2 (1.3%)	5 (1.6%)
Mild	53 (33.3%)	54 (34.4%)	107 (33.9%)
Moderate	85 (53.5%)	78 (49.7%)	163 (51.6%)
Severe	18 (11.3%)	23 (14.6%)	41 (13.0%)

gatifloxacin, are indicated to be dosed 3–8 times per day, respectively, for the first 2 days of therapy. From days 3–7, moxifloxacin is continued to be dosed 3 times per day and gatifloxacin is tapered to 4 times per day. The 1% azithromycin in DuraSite formulation supports a simplified dosing regimen that is tapered from twice a day to once daily. This is of clinical value for any patient.

It was of particular interest to learn whether 1% azithromycin in DuraSite can eradicate pathogens that are considered resistant to azithromycin as determined by CLSI systemic breakpoints. One problem with using these breakpoints to assess resistance is that they have never been evaluated in ocular tissue. In this study, 1% azithromycin in DuraSite eradicated pathogens that in vitro were resistant to azithromycin, erythromycin, and fluoroquinolones, suggesting that the systemic breakpoints may not be broadly applicable to ocular surface infections.

Table 3 Clinical resolution

	1% azithromycin in DuraSite (n = 159)	0.3% tobramycin (n = 157)	Difference (CI)	p value ^a
Visit 3				
Success	127 (79.9%)	123 (78.3%)	1.5	0.783
Failure	32 (20.1%)	34 (21.7%)	(–7, 4, 10.5)	

^ap value from Fisher Exact Test. Difference (azithromycin-tobramycin) and confidence interval (CI) for the difference in success rate is based on normal approximation for large samples without stratification by center.

Table 4 Clinical outcome

Global rating	1% azithromycin in DuraSite	0.3% tobramycin	p value ^a
Visit 2 (day 3–4)			
Resolution	37 (25.0%)	38 (25.7%)	0.488
Improved	102 (68.9%)	107 (72.3%)	
No Change	7 (4.7%)	3 (2.0%)	
Worse	2 (1.4%)	0	
Visit 3 (day 6 + 1)			
Resolution	127 (79.9%)	123 (78.3%)	0.743
Improved	30 (18.9%)	32 (20.4%)	
No change	0	1 (0.6%)	
Worse	2 (1.3%)	1 (0.6%)	

^ap values from Fisher Exact Test.

In addition to the majority of resistant *S. aureus* isolates, 1% azithromycin in DuraSite eradicated a strain of coagulase-negative *S. simulans* that was resistant to azithromycin, the fluoroquinolones, and oxacillin. Many reports show that oxacillin- and methicillin-resistant *S. aureus* are emerging causes of nosocomial and community-associated infections. Two oxacillin-resistant isolates were encountered and successfully eradicated in this study population. Others have reported that currently available formulations of oral azithromycin result in suboptimal efficacy against *S. pneumoniae* (Jacobs 2004; Hyde et al 2001). In this study, 1% azithromycin in DuraSite eradicated 60% of resistant *S. pneumoniae* from the ocular surface. Although the total number of resistant isolates in this study was small, these data indicate that the ocular preparation of 1% azithromycin in DuraSite has a broader killing spectrum than that usually attributed to azithromycin without DuraSite. These results require further study.

One other important consideration is that because the 1% azithromycin in DuraSite formulation is a gel-forming drop, it persists on the ocular surface longer than conventional aqueous eye drops. This enhances the bioavailability

Table 5 Bacterial eradication^a

	1% azithromycin in DuraSite (n = 159)	0.3% tobramycin (n = 157)	Difference (CI)	p value ^b
Visit 3				
Success	140 (88.1%)	148 (94.3%)	–6.2	0.073
Failure	19 (11.9%)	9 (5.7%)	(–12.4, 0.0)	

^aEradication was demonstrated as the absence in culture at visit 3 (day 6 + 1) of suprathreshold levels of pathogens that were found at baseline (visit 1, day 1).

^bp value from Fisher Exact Test.

Table 6 Eradication of drug resistant organisms by 1% azithromycin in DuraSite

Organism	Azithromycin	Erythromycin	Gatifloxacin	Moxifloxacin	Levofloxacin	Oxacillin
Total	72.4% (21/29)	70.4% (19/27)	50.0% (1/2)	50.0% (1/2)	50.0% (1/2)	100.0% (2/2)
<i>Staph aureus</i>	50.0% (2/4)	50.0% (2/4)	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)	N/A
<i>Staph epidermis</i>	100.0% (2/2)	100.0% (2/2)	100.0% (1/1)	100.0% (1/1)	100.0% (1/1)	100.0% (1/1)
<i>Staph simulans</i>	N/A	N/A	N/A	N/A	N/A	100.0% (1/1)
<i>Strep mitis</i>	100.0% (3/3)	100.0% (3/3)	N/A	N/A	N/A	N/A
<i>Strep mitis</i> group	100.0% (1/1)	100.0% (1/1)	N/A	N/A	N/A	N/A
<i>Strep oralis</i>	100.0% (2/2)	100.0% (2/2)	N/A	N/A	N/A	N/A
<i>Strep pneumoniae</i>	60.0% (9/15)	53.8% (7/13)	N/A	N/A	N/A	N/A
<i>Strep salivaris</i>	100.0% (1/1)	100.0% (1/1)	N/A	N/A	N/A	N/A
viridans <i>Strep</i>	100.0% (1/1)	100.0% (1/1)	N/A	N/A	N/A	N/A

N/A=Organisms without minimum inhibitory concentration result interpretation or resistant organism not available.

of azithromycin in the conjunctiva and potentially maximizes concentration-dependent azalide activity on the ocular surface.

There is a medical need for topical antibiotic choices in ophthalmology. Treatment failures may occur when patients dose at the wrong intervals, skip doses, or do not complete the full course of therapy. This in turn decreases the effectiveness of the immediate treatment and increases the likelihood that bacteria will develop resistance and will not be treatable by antibacterial drugs in the future. Patient and caregiver education is needed to make sure that antibiotics are taken as prescribed. The results of this clinical trial show that 1% azithromycin in DuraSite provides effective antibiotic coverage against the most common bacteria seen in bacterial conjunctivitis with a topical dosing regimen of just 7 drops.

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