Clinical Cure of Bacterial Conjunctivitis with Azithromycin 1%: Vehicle-Controlled, Double-Masked Clinical Trial

MARK B. ABELSON, WARREN HELLER, ARON M. SHAPIRO, ERWIN SI, PENG HSU, AND LYLE M. BOWMAN, ON BEHALF OF THE AZASITE CLINICAL STUDY GROUP

• PURPOSE: To analyze the effect of azithromycin 1% ophthalmic solution in DuraSite (InSite Vision, Inc, Alameda, California, USA) on bacterial conjunctivitis.

• DESIGN: Prospective, randomized, vehicle-controlled, parallel-group, double-masked multicenter clinical study.

• METHODS: Eligible male or female participants with a clinical diagnosis of acute bacterial conjunctivitis were randomized to either 1% azithromycin in DuraSite or vehicle for five days. Infected eyes were dosed twice daily on days 1 and 2 and once daily on days 3 through 5. Conjunctival cultures were obtained at baseline, visit 2 (day 3 or 4), and visit 3 (day 6 or 7). The primary end point was clinical resolution of signs and symptoms (rating of zero on ocular discharge, bulbar and palpebral injection) at visit 3. Efficacy measures were clinical resolution and bacterial eradication as evaluated in the per-protocol population. Safety was assessed by adverse events, slit-lamp findings, and ophthalmoscopy.

• RESULTS: Two hundred and seventy-nine participants (n = 130, 1% azithromycin in DuraSite; n = 149, vehicle), age one to 96 years, were evaluated for efficacy. Clinical resolution with azithromycin ophthalmic solution was statistically significant compared with that of vehicle ($P = .030$) at visit 3. Bacterial eradication rates with azithromycin ophthalmic solution reached 88.5% at visit 3 ($P < .001$) and included some pathogens resistant to azithromycin in vitro. Overall, adverse event rates were similar in both treatment groups.

• CONCLUSIONS: Azithromycin 1% ophthalmic solution in DuraSite showed statistically significant differences in clinical resolution and bacterial eradication rates when compared with vehicle. Because it was well tolerated in this population, it may be a viable treatment option for children and adults with bacterial conjunctivitis. (Am J Ophthalmol 2008;145:959–965.

THE MAIN ETIOLOGIC AGENTS IN BACTERIAL CONjunctivitis are *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.[1,2] Acute bacterial conjunctivitis infections often are self-limiting[3]; various health organizations report that the durations of infectivity and incubation depend on the organism, with infectivity lasting as many as 14 days and incubation lasting three to 29 days.[4,5] Topical antibiotics are used to speed recovery, to reduce spread to others and the chance of sequelae, and to prevent reinfection. Although a wide array of treatments currently are available for bacterial conjunctivitis, a topical antibiotic that delivers high bactericidal concentrations directly to the site of infection may provide an additional therapeutic treatment, especially in the case of resistant bacteria.

Azithromycin is an azalide antibiotic with broad-spectrum activity against gram-positive, gram-negative, and atypical bacteria.[6] To create a potentially long-acting topical eye drop, a solution of 1% azithromycin was formulated using the proprietary ocular delivery system DuraSite (InSite Vision, Inc, Alameda, California, USA). The solution of azithromycin 1% in DuraSite, AzaSite (Inspire Pharmaceuticals, Durham, North Carolina, USA), forms a stable mucoadhesive matrix that stays in contact with the conjunctiva and delivers active drug to the ocular surface over a period of several hours (Bowman LM, et al. IOVS 2007;48:ARVO E-Abstract 772). Preserved with benzalkonium chloride (BAK) 0.003%, this formulation can be dosed twice daily for the first two days and once daily for subsequent treatment days.[7] This treatment regimen, coupled with the delivery of a topically administered antimicrobial directly to the conjunctiva, may enhance patient convenience and improve compliance.[8,9]

The purpose of our phase 3 prospective, randomized, vehicle-controlled, double-masked, parallel-group, multicenter clinical trial was to compare the efficacy of the 1% ophthalmic solution of azithromycin in DuraSite with its vehicle in a five-day course of treatment for bacterial conjunctivitis, as indicated by the resolution of clinical signs and the eradication of causative bacteria.

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From Ophthalmic Research Associates, North Andover, Massachusetts (M.B.A., A.M.S.); Schepens Eye Research Institute, Harvard Medical School, Boston, Massachusetts (M.B.A.); Arizona Center for Clinical Trials, LLC, Phoenix, Arizona (W.H.); and InSite Vision, Inc, Alameda, California (E.S., P.H., L.M.B.).

Inquiries to Mark B. Abelson, Schepens Eye Research Institute, Harvard Medical School, 20 Staniford Street, Boston, MA 02114; e-mail: abelson@vision.eri.harvard.edu

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METHODS

ELIGIBLE PARTICIPANTS WERE MALE OR FEMALE, AGED ONE year or older, and had a positive clinical diagnosis of acute bacterial conjunctivitis with signs and symptoms present for fewer than three days. A best-corrected visual acuity (BCVA) score of 20/100 or better in each eye was also required for inclusion. A positive diagnosis of acute bacterial conjunctivitis required a minimum score of 1 (on a scale from 0 [absent/normal] to 3 [severe]) for ocular discharge and either bulbar or palpebral conjunctival injection in the same eye. Participants were excluded if any of the following criteria were present: debilitating disease, prior or concomitant use of any antibiotic or topical ophthalmic solution, suspected viral or allergic conjunctivitis, or positive pregnancy test results. All participants read and signed an Institutional Review Board-approved informed consent form prior to study entry.

Qualified participants were randomized in block format to receive either vehicle or 1% azithromycin in DuraSite in the qualified eye(s) twice daily on days 1 and 2 and once daily on days 3 through 5. An equal probability randomization procedure was used. Vehicle was identically supplied and formulated except that it contained no azithromycin. Study personnel and participants were masked from their treatment assignments. Only the study statistician and data-monitoring committee saw unmasked data, but these team members did not have any contact with study participants.

Signs of bacterial conjunctivitis—palpebral conjunctival injection, bulbar conjunctival injection, and ocular discharge—were measured at each visit: visit 1 (day 1, study entry), visit 2 (day 3 or 4), and visit 3 (day 6 or 7). Both follow-up visits occurred at least 12 hours after the previous dose of study medication. Conjunctival injection was graded by clinical investigators using the Ophthalmic Research Associates (ORA) Bacterial Conjunctivitis Bulbar and Palpebral Redness Grading Scales (ORA, North Andover, Massachusetts, USA), from 0 (absent/normal) to 3 (severe). A slit-lamp biomicroscopy examination was performed at each visit, and BCVA also was measured. An undilated ophthalmoscopy examination was performed at the first and last visit.

Eyes with a positive diagnosis of acute bacterial conjunctivitis were cultured at each visit before the administration of study medication. Conjunctival bacterial cultures were taken by the clinical investigator from the cul de sac using a sterile Dacron swab and were transported in a sterile phosphate buffered saline, pH 7.2, with 20% glycerol medium to an independent laboratory. Upon arrival at the laboratory, a serial dilution was performed on the specimen, and aliquots of these dilutions were inoculated onto bacteriologic media (5% sheep blood agar and chocolate agar) and were incubated at 35 C in 5% CO_2. The identification and quantification of colonies of all pathogens were recorded after 48 hours of incubation. Positive culture results were determined by previously defined minimum threshold bacterial counts.[10]

Minimum inhibitory concentrations (MICs) of azithromycin were evaluated for certain clinical isolates. The objective was to determine: 1) the range of MICs for azithromycin-resistant clinical isolates and 2) whether pathogens resistant to azithromycin according to the Clinical Laboratory and Standards Institute (CLSI) systemic breakpoint recommendations could be eradicated by treatment with 1% azithromycin ophthalmic solution in DuraSite.

The primary efficacy variable, clinical resolution, was evaluated at the test-of-cure visit (visit 3 on day 6 or 7) in the per-protocol population, defined as all randomized subjects who received at least one drop of the study medication and who had baseline culture results indicating pathogenic bacteria levels. Clinical resolution was defined as the absence of the three clinical signs (ocular discharge, bulbar conjunctival injection, and palpebral conjunctival injection). The secondary efficacy variable was bacterial eradication at visit 3, as indicated by the absence of bacterial growth. Bacterial outcome was scored categorically from 0 (eradicated) to 3 (worsening) compared with baseline. Supportive analyses included a tabulation of bacterial eradication rates and clinical resolution rates by treatment, gram stain, and baseline organism.

All subjects enrolled in the study who received at least one-dose of the study medication were evaluated for safety. Safety was assessed by the incidence of adverse events (AEs) and changes in BCVA, biomicroscopy, and ophthalmoscopy. All AEs and ocular AEs occurring in more than 5% in either treatment group were summarized. Ocular AEs were classified as ocular burning or stinging or foreign body sensation on instillation, other subject-reported ocular changes, clinically significant worsening of BCVA, and treatment-emergent changes observed with biomicroscopy and ophthalmoscopy.

All data analysis was carried out according to a preestablished analysis plan. Superiority over vehicle was shown where $P < .05$ for treatment differences. The planned target enrollment was set at 560 participants (to enroll at least 224 participants with bacterially confirmed conjunctivitis, with 112 per treatment group) calculated based on a power of 0.90 and $\alpha = 0.05$. The primary analysis was the 95% confidence interval (CI) and the Fisher exact test for the clinical resolution difference among per-protocol participants. The same statistical tools were used to analyze bacterial eradication. If data were missing for visit 3 (last efficacy visit), a last observation carried forward method was used.

RESULTS

STUDY PARTICIPANTS WERE ENROLLED AT 58 CLINICAL centers in the United States, Mexico, Guatemala, and the Dominican Republic between August 6, 2004 and January 19, 2006. A total of 685 participants were enrolled. Of

TABLE 1. 1% Azithromycin in DuraSite Vehicle-Controlled Trial for Bacterial Conjunctivitis: Patient Disposition

	Azithromycin in DuraSite (n = 335)	Vehicle (n = 350)	Total (n = 685)
Total number of patients			
Randomized	335 (100%)	350 (100%)	685 (100%)
Completed	313 (93.4%)	317 (90.6%)	630 (92%)
Discontinued	22 (6.6%)	33 (9.4%)	55 (8.0%)
Primary reason for discontinuation			
Adverse event	2 (0.6%)	5 (1.4%)	7 (1.0%)
Protocol violation	1 (0.3%)	4 (1.1%)	5 (0.7%)
Withdrew consent	6 (1.8%)	6 (1.7%)	12 (1.8%)
Lost to follow-up	5 (1.5%)	1 (0.3%)	6 (0.9%)
Lack of efficacy	7 (2.1%)	15 (4.3%)	22 (3.2%)
Treatment unmasked	1 (0.3%)	0 (0.0%)	1 (0.1%)
Other	0 (0.0%)	2 (0.6%)	2 (0.3%)

TABLE 2. 1% Azithromycin in DuraSite Vehicle-Controlled Trial for Bacterial Conjunctivitis: Age of Safety Population

Age (yrs)	Azithromycin in DuraSite (n = 333)	Vehicle (n = 350)	Total (n= 683)	*P* value*
Mean (SD)	31.0 (23.2)	31.0 (23.9)	31.0 (23.5)	.970
Median (range)	28 (1 to 84)	29 (1 to 96)	28 (1 to 96)	
Pediatric (1 to 11)	90 (27.0%)	94 (26.9%)	184 (26.9%)	
Nonpediatric (≥ 12)	243 (73.0%)	256 (73.1%)	499 (73.1%)	> .999
Nongeriatric (< 65)	296 (88.9%)	310 (88.6%)	606 (88.7%)	
Geriatric (≥ 65)	37 (11.1%)	40 (11.4%)	77 (11.3%)	.904

SD = standard deviation.
**P* value for age from *F* test from an analysis of variance model containing term for treatment.

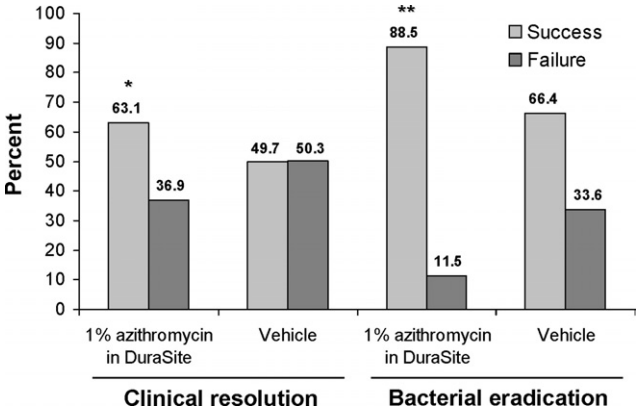

FIGURE 1. Bar graph demonstrating per-protocol efficacy analysis, with last observation carried forward. N=279 patients treated with either AzaSite n=130 or vehicle n=149. The clinical resolution and bacterial eradication rates observed were statistically in favor of AzaSite. *P < .030, **P < .001.

TABLE 3. 1% Azithromycin in DuraSite Vehicle-Controlled Trial for Bacterial Conjunctivitis: Summary of Adverse Events with Frequency ≥ 1%*

	Azithromycin in DuraSite (n = 333)	Vehicle (n = 350)	Total (n = 683)
Eye irritation	5 (1.5%)	1 (0.3%)	6 (0.9%)
Worsening bacterial conjunctivitis	5 (1.5%)	3 (0.9%)	8 (1.2%)
Headache	4 (1.2%)	8 (2.3%)	12 (1.8%)
Pharyngolaryngeal pain	4 (1.2%)	2 (0.6%)	6 (0.9%)
Conjunctival edema	2 (0.6%)	5 (1.4%)	7 (1.0%)

*No *P* values were calculated.

these, only two were excluded from the safety population because they received incorrect study medications. Of the 685 randomized participants, 335 received active treatment and 350 received vehicle. A total of 630 participants (92%) completed the study (Table 1). More than twice as many in the vehicle group were discontinued early because of lack of efficacy 15/350 (4.3%) than in the active treatment group seven/335 (2.1%).

The mean age of the safety population (n = 683) was 31 years. Approximately 184/683 (27%) of the treated group were pediatric (age, one to 11 years) and 77/683 (11%) were older than 65 years (Table 2). There were no significant differences between the treatment groups in age, gender, race, or eye color.

There were 279 participants in the per-protocol group (1% azithromycin in DuraSite, n = 130; vehicle, n = 149). The clinical resolution rates at visit 3 were 63.1% for the active drug and 49.7% for vehicle ($P = .030$, Fisher exact test; difference, 13.4%; 95% CI, 1.9% to 25.0%). Bacterial eradication rates measured at visit 3 (day 6 or 7) were 88.5% for 1% azithromycin ophthalmic solution and 66.4% for vehicle ($P < .001$, Fisher exact test; difference, 22.0%; 95% CI, 12.7% to 31.4%; see Figure 1).

The overall AE rate was 41/333 (12.3%) for the group treated with 1% azithromycin in DuraSite and 42/350 (12.0%) for the vehicle group. AEs were judged possibly or probably related to treatment in 13/333 (3.9%) of participants in the group that received the azithromycin ocular solution. In this study, the frequency of each ocular AE experienced with 1% azithromycin in DuraSite was less than 2% [2 to 5 events/333] (Table 3). There were no

TABLE 4. 1% Azithromycin in DuraSite Vehicle-Controlled Trial for Bacterial Conjunctivitis: Summary of Ophthalmic (Biomicroscopy and Ophthalmoscopy) Changes at Visit 3

	Azithromycin in DuraSite (n = 333)	Vehicle (n = 350)
Conjunctival chemosis	13 (3.9%)	19 (5.1%)
Lids swelling	13 (3.9%)	29 (8.3%)
Lids other	11 (3.3%)	14 (4.0%)
Conjunctiva other	9 (2.7%)	9 (2.6%)
Cornea staining/erosion	7 (2.1%)	10 (2.9%)
Lens cataracts	3 (0.9%)	0 (0.0%)
Cornea edema	2 (0.6%)	6 (1.7%)
Cornea infiltrates	2 (0.6%)	5 (1.4%)
Cornea vascularization	2 (0.6%)	1 (0.3%)
Anterior chamber cells	1 (0.3%)	1 (0.3%)
Anterior chamber flare	1 (0.3%)	0 (0.0%)
Anterior chamber synechiae	1 (0.3%)	0 (0.0%)
Cornea other	1 (0.3%)	0 (0.0%)
Fundus pathologic features	1 (0.3%)	1 (0.3%)
Vitreous pathologic features	0 (0.0%)	2 (0.6%)

serious AEs reported by participants in the active group. Two participants in the vehicle group reported serious AEs unrelated to treatment (corneal ulcer and a cerebrovascular event).

Only one participant (0.3%) in the 1% azithromycin in DuraSite group and six participants (1.1%) in the vehicle group had clinically significant worsening of BCVA (≥ three-line change Snellen chart) at visit 3. The most frequent biomicroscopic changes in the azithromycin-treated group were conjunctival chemosis (3.9%) and eyelid swelling (3.9%). Each of these changes occurred more frequently in the vehicle group (5.1% and 8.3%, respectively; Table 4).

A supportive analysis of bacterial eradication relative to baseline bacterial gram stain showed that the active drug resulted in higher eradication rates than vehicle for gram-negative (91.4% vs 78.6%) and gram-positive (89.4% vs 60.6%) bacteria. Of the gram-positive organisms, *S. aureus* was eradicated in 82.6% of active-treated participants but in just 40.9% of the vehicle-treated participants, and *S. pneumoniae* was eradicated in 94.4% of active-treated participants vs in 77.8% of vehicle-treated participants. The gram-negative organism *H. influenzae* was eradicated in 36/39 (92.3%) and 29/38 (76.3%) of participants in the active- and vehicle-treatment groups, respectively. At the test-of-cure visit, 1% azithromycin ophthalmic solution eradicated more than 90% of *H. influenzae*, *S. pneumoniae*, *Staphylococcus epidermidis*, and *Streptococcus mitis* group pathogens isolated from the per-protocol population (Figure 2).

For the MIC analysis, bacteria that were isolated from the per-protocol group were grown in culture and were exposed to azithromycin and other antibiotics used in commercial eye drop preparations. The MIC is the lowest

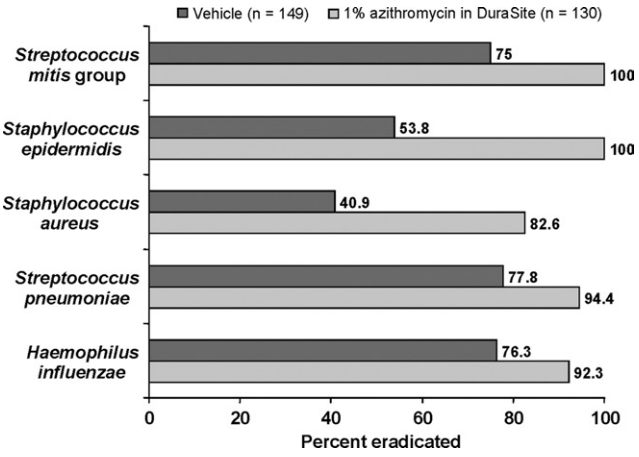

FIGURE 2. Bar graph demonstrating rate of eradication of top five most frequently cultured bacteria.

concentration of antibiotic that would inhibit growth of the tested bacterial isolates. MIC_{50} indicates the antibiotic concentration that would inhibit growth of 50% of the tested isolates; MIC_{90} represents the concentration that would inhibit growth of 90% of the tested isolates.[11] The most prevalent gram-positive bacteria cultured in this study was *S. pneumoniae* (n = 129), followed by *S. aureus* (n = 65) and *S. epidermidis* (n = 27). Among gram-negative bacteria, *H. influenzae* (n = 135) was the most common. The overall azithromycin MIC_{50} and MIC_{90} against all bacterial pathogens isolated were 1 μg/ml and 256 μg/ml, respectively. The MIC_{50} was 0.12 μg/ml and the MIC_{90} was > 1024 μg/ml against azithromycin-resistant *S. pneumoniae*. The MIC_{50} and MIC_{90} for azithromycin against *S. aureus* were 2 μg/ml and > 1024 μg/ml, respectively. The presence of the oxacillin-resistant phenotype increased the azithromycin MIC_{50} to 256 μg/ml. *H. influenzae* had an azithromycin MIC_{50} of 1 μg/ml and a MIC_{90} of 2 μg/ml, which are within the CLSI susceptibility breakpoint of 4 μg/ml for this species.

Overall, 1% azithromycin in DuraSite eradicated 85% (23/27) of the azithromycin-resistant pathogens isolated, including 92% (11/12) of *S. pneumoniae* strains. Azithromycin in DuraSite also eradicated a small number of resistant *S. aureus*, *S. epidermidis*, and *S. mitis* strains encountered in the clinical study (Table 5) and those *S. epidermidis* strains that were resistant to oxacillin and third- and fourth-generation fluoroquinolones. 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*).

DISCUSSION

IN ITS CURRENTLY AVAILABLE FORMULATIONS—PILL, ORAL suspension, and intravenous—azithromycin (Pfizer, Inc,

TABLE 5. Summary of Azithromycin-Resistant Bacteria Eradicated at Visit 3 by 1% Azithromycin in DuraSite

Organism	MIC Range (μg/μl)	No. of Resistant Strains	Rate of Bacterial Eradication at Visit 3
Staphylococcus aureus	1 to > 1024	8	62.5%
Staphylococcus epidermis	0.5 to > 1024	2	100%
Streptococcus mitis group	0.03 to > 1024	3	100%
Streptococcus oralis	1	1	100%
Streptococcus pneumoniae	0.06 to 1024	12	91.7%
Viridans streptococcus	4	1	100%

MIC = minimum inhibitory concentration.

New York, New York, USA) is used to treat dermal, respiratory, and sexually transmitted bacterial infections. Two phase 3, parallel-group, controlled clinical trials were conducted to study the efficacy of the 1% azithromycin in DuraSite for the resolution of signs and symptoms in participants with acute bacterial conjunctivitis. A report from the active-controlled trial comparing the clinical and bacterial resolution rates in 316 participants treated for five days with either 0.1% tobramycin drops (four times daily) or 1% azithromycin in DuraSite (two drops on days 1 and 2, one drop on days 3 through 5) showed that the microbial eradication and clinical cure rates were equivalent to the aminoglycoside.[12]

This article reports the comparison of 1% azithromycin in DuraSite with vehicle. The results were obtained with a dosing regimen identical to that used in the active trial and show that treatment with 1% azithromycin in DuraSite for five days resulted in clinical cure and the eradication of causative pathogens at visit 3. Eradication rates for the most common causative pathogens, *S. pneumoniae*, *H. influenzae*, and *S. aureus*, ranged from 82.6% to 94.4%. The clinical resolution and microbial efficacy rates at the test-of-cure visit were significantly greater than those attained in the vehicle-controlled population. Higher bacterial eradication rates were observed with 1% azithromycin ophthalmic solution than vehicle for gram-negative (91.4% vs 78.6%) and gram-positive (89.4% vs 60.6%) bacteria, indicating a broad spectrum of microbial activity.

The overall eradication rate of 1% azithromycin in DuraSite against bacteria with MIC of > 1024 μg/ml was 78% (67% for *S. aureus* and 100% for *S. epidermidis*, *S. pneumoniae*, and *S. mitis*). Although standard in vitro susceptibility testing is important in the management of infectious diseases, MIC values should be interpreted in light of the expected delivery and drug concentration at the site of infection. This point may be especially important for ocular infections treated topically, where local concentrations of antibiotic may be much higher than maximum serum levels obtained from systemic dosing. It should be noted that published breakpoints are based on the CLSI standards and may not be applicable to topical ophthalmic preparations.[11] Standards specific to ocular tissues have not yet been developed.

Treatment with 1% azithromycin in DuraSite led to the eradication of 85% (23/27) of the azithromycin-resistant pathogens. Romanowski and associates demonstrated the proof of principle that in vitro antibiotic resistance (per CLSI standards) does not always correlate with in vivo ocular treatment failure. According to the authors, an aggressive treatment regimen with gatifloxacin 0.3% seemed to overcome in vitro resistance and resulted in successful treatment of gatifloxacin-resistant *S. aureus* keratitis in the New Zealand white rabbit keratitis model.[13] In our study, the laboratory analysis of the eradication pattern of azithromycin ophthalmic formulation indicates a broader spectrum of activity than that normally seen with azithromycin, lending support to Romanowski and associates' proof of principle. Further, the ability of 1% azithromycin ophthalmic solution to eradicate pathogens resistant to azithromycin may be the result of the high conjunctival levels achieved by topically administering antimicrobials directly to the conjunctiva. It therefore is likely that MIC determinations using standard in vitro methods underestimate the ability of azithromycin to eradicate bacteria in vivo. Additional investigation to elucidate the reasons for this discrepancy currently is underway.

The safety profile of 1% azithromycin in DuraSite was evaluated and compared with that of vehicle. Ocular AEs such as stinging and burning were rare, and the incidence rate of eye irritation was less than 2%. Eye irritation in the active treatment group was mild. In addition, the formulation contains a minimal amount of BAK preservative at 0.003% (w/v); in some cases, higher levels of BAK have been associated with ocular cytotoxicity.[14,15] However, the BAK concentration and regimen used in this study have not shown previously any ocular cytotoxicity in humans.[16] The data suggest that the preserved formulation of 1% azithromycin ophthalmic solution used in this study was well tolerated. Changes in other safety parameters were seen in approximately 2% or less of participants in both treatment groups and were not considered clinically relevant.

Azithromycin's favorable pharmacokinetics (i.e., accumulation in tissue and uptake by cells) and the ability

of DuraSite delivery vehicle to prolong ocular retention time enable a convenient dosing regimen of twice daily on days 1 and 2 and once daily on days 3 through 5 (Keller N, et al. IOVS 1993;34:ARVO Abstract 3907).[17] The outcomes in clinical trials of this simplified dosing regimen may be explained by the presence of a high concentration of the antibiotic at the ocular surface that provides appropriate drug levels early in the course of infection. The ocular preparation seems to be just as effective against gram-positive and gram-negative organisms as against azithromycin-insensitive or -resistant pathogens. This represents a nontrivial improvement in the eradication spectrum of the azithromycin solution and warrants further clinical investigation.

Many bacterial conjunctivitis infections resolve without antibiotic treatment, and proper hygiene alone can curb greatly the spread of infectious disease in the community. In addition, the indiscriminate use of antibiotics may lead to colonization by drug-resistant organisms. However, as soon as a bacterial infection has been communicated, shortening its period of infectivity can benefit those at risk for complications and can reduce the chance for further transmission. Ocular antibiotics that eradicate bacteria on the ocular surface and resolve clinical signs and symptoms with simple dosing regimens are useful tools for the prevention of ocular sequelae and bacterial resistance. Azithromycin 1% ophthalmic solution in DuraSite showed statistically significant differences in clinical resolution and bacterial eradication rates when compared with vehicle in children and adults. Because it was well tolerated in this population, it may be a viable treatment option for bacterial conjunctivitis.

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THE AZASITE CLINICAL STUDY GROUP

● **A list of the members of the AzaSite Clinical Study Group:** Marc Abrams, Stacey Ackerman, Alejandro Jose Aseff-Zamorano, Jason Bacharach, James D. Brauch, Donald Cerise, Thomas Coeonado, Jerome Crampton, Jung Dao, William Davitt, Jesse DeLeon, Vincent DeLuise, Brian Desmond, Harvey DuBiner, Richard Eiferman, Lamont Ericson, Richard Evans, James Felch, Jesus M. Feris-Iglesias, John Foley, Sergio Anibal Galdamez-Coronado, Paul Galentine, Joel Gegffin, Casimiro Gonzales, Juan Luis Gonzalez-Trevino, Robert Groat, Russell Harral, Warren Harvey Heller, Thomas Henderson, Bruce Kanengiser, Mustapha Kibirige, Alexandra Kostick, Roberto Leal Leyva, Fausto Miguel Lechuga-Ortiz, Richard Leung, James Liu, Douglas Long, Arash Mansouri, Carlos Martinez, Mark Mayo, David M. McGarvey, Elizabeth Mitchell, Francisco Jose Montiel-Viesca, C. Thomas Moran, Kenneth Olander, Melinda O'Rourke, Don Perez-Ortiz, Adib Federico Rodriguez-Solares, Guillermo Estuardo Rosales-Andrino, Michael Rotberg, Jay Rubin, Mark Rubin, Marc Sanders, Howard Schenker, David Shulman, Bruce Silverstein, Steven Silverstein, Herbert S. Stern-Diaz, Dara Stevenson, Nighat Sultana, James Sutton, Michael Trepedino, Monica C. Thorman-Peynado, Jose Alfredo Vazquez-Diaz, Francis Wapner, Susan Watson, Robert Williams, and Michael Yaros.

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