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A clinical comparison of two formulations of tobramycin 0.3% eyedrops in the treatment of acute bacterial conjunctivitis

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PURPOSE. *To compare the safety and efficacy of a new enhanced viscosity ophthalmic formulation of tobramycin, given twice daily (BID), with the existing four times daily (QID) treatment regimen in patients with acute bacterial conjunctivitis.*
METHODS. *This was a 12-day, multicenter, observer-masked, randomized, parallel group study. Patients received one drop of tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution BID or tobramycin 0.3% (3 mg/mL) ophthalmic solution QID in the affected eyes for 7 days. The primary efficacy variable was the percentage of patients with sustained cure/presumed bacterial eradication based on clinical judgment at the test-of-cure visit (Day 12). Pretherapy bacterial isolates were obtained and tested for susceptibility to tobramycin by determination of minimum inhibitory concentrations (MIC).*
RESULTS. *A total of 276 patients were enrolled in the study and 203 of these were culture positive and attended all follow-up examinations. In this group, 98% of those treated with tobramycin enhanced viscosity ophthalmic solution and 99% of those treated with tobramycin 0.3% ophthalmic solution were categorized as having sustained cure/presumed eradication at the test-of-cure visit (p=0.6037). Reported adverse events were not serious, mild to moderate in severity, and generally did not prevent continuation in the study. Several pretreatment pathogens demonstrated tobramycin resistance (MIC > 4 mg/mL). However, therapy with both treatments was effective in the majority of the cases.*
CONCLUSIONS. *Tobramycin enhanced viscosity ophthalmic solution is well tolerated and has equivalent efficacy to the established treatment regimen with a simplified posology. The formulation provides an alternative therapy for acute bacterial conjunctivitis that should improve patient compliance and satisfaction. (Eur J Ophthalmol 2005; 15: 541-9)*

KEY WORDS. *Acute conjunctivitis, Bacterial conjunctivitis, Tobramycin, Enhanced viscosity eyedrops*

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INTRODUCTION

Acute conjunctivitis is the most common ocular infection in children (1) and is also common in adults. Although it is generally self-limiting, treatment with topical ophthalmic antibiotics is normally recommended as it hastens resolution of the disease, decreases morbidity, helps to prevent recurrence, and reduces the risk of progression to more serious corneal disease (2-4). Since it is generally impractical to wait for culture results before commencing treatment for acute bacterial conjunctivitis, it is common practice to prescribe a broad-spectrum antibiotic agent covering both Gram-positive and Gram-negative organisms (2, 4).

Tobramycin, a broad-spectrum aminoglycoside antibiotic, has been used for the topical treatment of ocular infections since 1981. Tobramycin 0.3% has been demonstrated to be equivalent in efficacy to other drugs used to treat bacterial conjunctivitis, such as gentamicin (5), ciprofloxacin (6, 7), ofloxacin (8), norfloxacin (9), and fusidic acid (10). Evidence of extensive development of resistance to the drug in common ocular pathogens is lacking, despite widespread use for a prolonged period of time (11, 12).

The aim of antimicrobial therapy in any infectious disease is to provide a high concentration of antibiotic rapidly at the area of infection and to maintain a level that is at least inhibitory for as long as possible (2). This often necessitates frequent dosing. The recommended dosage regimen for the current, commercially available formulation of tobramycin eyedrops (tobramycin 0.3% [3 mg/mL] ophthalmic solution), in acute bacterial conjunctivitis, is one to two drops given four times daily (QID) (13). Patient compliance with such a dosage regimen may represent a problem, particularly in pediatric patients (10). A new ophthalmic formulation, tobramycin enhanced viscosity ophthalmic solution, has been developed to reduce the current recommended dosage regimen. The formulation has been designed to prolong ocular retention of tobramycin, so that antibacterial coverage is maintained with a simplified twice-daily (BID) posology.

Pharmacokinetic studies, conducted in rabbits and man, have demonstrated an improved pharmacokinetic profile in tears for the new formulation when compared to tobramycin 0.3% (3 mg/mL) ophthalmic solution (14). A pharmacokinetic study in humans has also demonstrated the safety and tolerance of the new formulation in healthy volunteers, during once daily administration over 9 days (14).

The present report concerns a large-scale clinical study

TABLE I - DEMOGRAPHIC DETAILS OF ALL PATIENTS PROVIDING A CONJUNCTIVAL SPECIMEN ON DAY 1, BY TREATMENT GROUP

	Total		**Tobramycin 0.3% (3 mg/mL) enhanced viscosity solution**		**Tobramycin 0.3% (3 mg/mL) ophthalmic solution**	
	N	**%**	**N**	**%**	**N**	**%**
Age, yr						
1-11	6	2.19	4	2.92	2	1.46
12-17	1	0.36	0	0.00	1	0.73
18-64	181	66.06	94	68.61	87	63.50
>65	86	31.39	39	28.47	47	34.31
65-<75	39	45.35	19	48.72	20	42.55
75-<85	39	45.35	18	46.15	21	44.68
85-<95	8	9.30	2	5.13	6	12.77
≥95	0	0.00	0	0.00	0	0.00
Sex						
Male	110	40.15	62	45.26	48	35.04
Female	164	59.85	75	54.74	89	64.96
Race						
White	268	97.81	134	97.81	134	97.81
Black	1	0.36	1	0.73	0	0.00
Asian	5	1.82	2	1.46	3	2.19

comparing the efficacy of tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution with tobramycin 0.3% (3 mg/mL) ophthalmic solution in patients from countries throughout Europe who had a diagnosis of acute bacterial conjunctivitis based on clinical observation. In addition, bacterial isolates obtained from patients in this study were identified to strain level and subjected to in vitro determination of their minimum inhibitory concentration for tobramycin (MIC) to confirm susceptibility to the antibiotic.

METHODS

Study design

This was a 12-day, multicenter, observer-masked, randomized, parallel-group study designed to evaluate the efficacy and safety of tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution compared to tobramycin 0.3% (3 mg/mL) ophthalmic solution. Although it is generally recommended that confirmatory trials in anti-infective therapy be double-masked, such a design was not practical when comparing the new BID regimen with the established QID dosing schedule. Adoption of a double-masked design, in which a placebo product would also have been used for alternate doses in the tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution group, may have diluted the drug concentration and could itself have had an antibacterial effect due to the preservative used in the formulation and the washing of bacteria from the eye. A total of 41 principal investigators, distributed throughout Europe, from Finland in the north to Greece in the south, participated in the study.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. All investigational sites obtained appropriate ethics committee review and approval of the protocol prior to enrolling any patient. Written informed consent was obtained from all participants (or parent/guardian for patients under 18 years of age).

TABLE II - FINAL CLINICAL JUDGEMENT AT THE TEST-OF-CURE VISIT (PP DATA SET)

Treatment	Total	Sustained cure/ presumed eradication		Relapse/ failure	
	N	N	%	N	%
Tobramycin 0.3% (3 mg/mL) enhanced viscosity solution	96	94	97.92	2	2.08
Tobramycin 0.3% (3 mg/mL) solution	107	106	99.07	1	0.93
Total	203	200	98.52	3	1.48

p=0.6037 (Fisher's exact test for treatment group comparison); PP = Per protocol

TABLE III - CLINICAL CURE RATE BETWEEN TREATMENTS BY SEVERITY OF CLINICAL SIGNS (PP DATA SET)

	Tobramycin 0.3% (3 mg/mL) enhanced viscosity solution				Tobramycin 0.3% (3 mg/mL) solution				p value*
	Clinically cured				Clinically cured				
	Yes		No		Yes		No		
Severity grade	N	%	N	%	N	%	N	%	
Not severe	81	97.59	2	2.41	96	98.97	1	1.03	0.4726
Severe	13	92.86	0	0	10	100	0	0	N/A
Total	94	97.92	2	2.08	106	99.07	1	0.93	

*Cochran-Mantel-Haenszel
PP = Per protocol

Patients

Patients diagnosed with bacterial conjunctivitis based on clinical observation, who were at least 1 year of age, were eligible for inclusion. Women of childbearing potential participated only if they were not lactating, had a negative pregnancy test prior to entry into the study, and agreed to use birth control methods throughout the study.

Patients with any of the following conditions were excluded: contact lens use during the course of the study; only one sighted eye or vision not correctable to 0.6 logMAR or better in both eyes; suspected fungal, viral, or acanthamoeba infection; current use of any preserved topical ophthalmic medication; known or suspected allergy or hypersensitivity to aminoglycosides, ocular preservatives, or any components of the study medication; any systemic or ocular disease or disorder, complicating factors, or structural abnormality that would negatively affect the conduct or outcome of the study; use of an ocular or oral antibacterial agent within the 7 days prior to the study or during the study; use of systemic/topical steroidal and non-steroidal anti-inflammatory agents within 7 days prior to study entry or during the study; current substance abuse problems or history of substance abuse; participation in any other investigational clinical study within the previous 30 days; any historical or current immunosuppressive disorder or use of immunosuppressive therapy (including chemotherapy); and current corneal ulceration or stromal infiltration.

Intervention

Patients were randomized to receive one of two medications: tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution or commercially available tobramycin 0.3% (3 mg/mL) ophthalmic solution (TOBREX, Alcon Laboratories) in an equal ratio (1:1). Patients were randomized sequentially at each investigational site.

One drop of the medication was instilled in the eye QID for tobramycin 0.3% (3 mg/mL) ophthalmic solution or BID for tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution, for 7 days (± 1 day). Those patients randomized to receive tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution and assessed as having severe disease were instructed to dose four times daily for the first day, followed by twice daily dosing for the remainder of treatment. The test articles were supplied in identical appearance, masked containers identified by an investigator and patient number.

Four patient visits were planned in the study: Day 1 (screening visit); Day 3; Day 7; and Day 12 (test-of-cure visit).

Main outcome measures and methods

- Efficacy. The primary efficacy variable assessed was the percentage of patients with sustained cure/presumed bacterial eradication based on final clinical judgment at the test-of-cure visit. The secondary efficacy variables assessed were lid erythema/swelling, palpebral conjunctiva, bulbar conjunctiva, conjunctival discharge/exudate, tearing, and epithelial disease. These variables were measured on a four point scale (absent = 0; mild = 1; moderate = 2; severe = 3). In addition, an overall physician's impression relative to Day 1 on a four-point scale (cured = 0; better = 1; unchanged = 2; worse = 3) was made at the subsequent three visits. If, at the test-of-cure visit, any of the signs or symptoms of bacterial

TABLE IV - SUMMARY OF PRETHERAPY BACTERIAL ISOLATES OBTAINED FROM EYES OF ENROLLED PATIENTS

Species	Total pretherapy isolates*	Single isolate count†
S. aureus	52	31
S. epidermidis	197	142
Other staphylococci	28	18
S. pneumoniae	36	26
Other Gram-positive species	31	6
H. influenzae	22	15
P. aeruginosa	5	4
Enterobacteriaceae	25	15
Other Gram-negative species	26	8

*All isolates obtained from 340 culture-positive eyes (includes polymicrobic cultures)
†Single isolate recovered per eye

conjunctivitis, absent on the last day of therapy, had reappeared or there was evidence of bacterial infection remaining or recurring, then the treatment was considered a treatment failure.

Best-corrected visual acuity was measured in logMAR values at each visit. The measurement obtained on Day 1 was defined as the baseline measurement. Clinically relevant changes in visual acuity were defined as a decrease of three or more logMAR lines from baseline and were reported as adverse events.

Patients who showed no clinically relevant response to the medication or who worsened after at least 2 days on full treatment were defined as treatment failures. These patients were discontinued from their assigned study medication, exited from the study, and provided alternate therapy.

- Microbiology. A microbiological specimen was taken from the entire surface area of the lower conjunctiva of the affected eyes at the Day 1 visit, using a sterile disposable culture collection and transport system. If the infection occurred in only one eye, only the infected eye was swabbed. Specimens were processed at a designated clinical microbiology laboratory within 24 hours of collection whenever possible. Patients classified as treatment failures had swabs taken at exit from the study. Pretherapy bacterial isolates were identified by species and strain and tested for susceptibility to tobramycin by determination of MIC. Tests were performed in accordance with National Committee for Clinical Laboratory Standards guidelines (NCCLS, US).
- Safety. The evaluation of safety was conducted on all patients who entered the study and received at least one dose of study drug. The safety analysis was based on an evaluation of the extent of exposure to the study drug, adverse events, and visual acuity.

Statistical analysis

Since the trial was designed to detect equivalence (no difference between the two treatments), primary inference for efficacy was based on the per protocol (PP) data set. This data set included all randomized patients who received drug, met the inclusion criteria, were culture positive on Day 1, and were present for all study visits. If the 95% confidence limits for the difference between treatments in presumed bacterial eradication rate were within ±20%, then the tobramycin formulations were declared equivalent. The enrollment target was set at 104 culture-positive patients per group. This provided the study with a 90% power that the 95% confidence interval (CI) for the difference between treatments in presumed bacterial eradication rate was within ±20% (assuming eradication rate at test-of-cure visit for tobramycin 0.3% [3 mg/mL] ophthalmic solution equals 80%). To confirm the robustness of the results obtained from the PP data set, a separate efficacy analysis based on all randomized patients who were culture positive on Day 1 was also conducted (modified intent to treat analysis [MITT]).

For the secondary efficacy variables (overall physician's impression, erythema/swelling, palpebral conjunctiva, bulbar conjunctiva, conjunctival discharge/exudate, and tearing), a Cochran-Mantel-Haenszel test, based on rank scores and controlling for centers, was used to compare the mean scores between treatments at each visit. If both

TABLE V - SUSCEPTIBILITY PROFILE OF PRETHERAPY ISOLATES OF MAJOR BACTERIAL SPECIES TO TOBRAMYCIN

	S. aureus	***S. epidermidis***	***S. pneumoniae***	***H. influenzae***
Range (µg/mL)	0.06->64	0.008->64	8–64	4–16
MIC_{50} (µg/mL)	0.5	0.13	16	8.0
MIC_{90} (µg/mL)	2.0	2.0	32	8.0
Susceptibility breakpoints*	>4.0	>4.0	>4.0	>4.0
% Susceptible strains	91	80	0	13
Acquired resistance breakpoints†	8.0	2.0	256	128
% Strains with acquired resistance	9	20	0	0

*US National Committee for Clinical Laboratory Standards systemic defined breakpoint
†Acquired resistance breakpoint defined as equal to MIC_{50} x 16

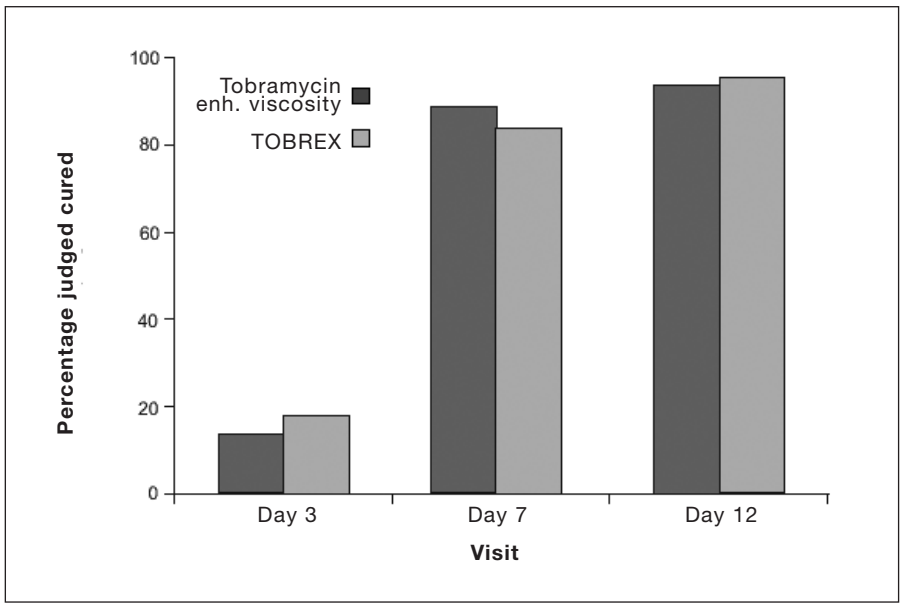

Fig. 1 - *Percentage of patients judged cured (physician's impression) by visit (PP data sert).*

eyes were infected, the worse eye (or the right eye in case of equal severity) was chosen for statistical analysis.

RESULTS

Patient demographics

A total of 276 patients were enrolled. A total of 274 patients had conjunctival specimens collected on Day 1 and 254 of these were found to be culture positive. A total of 203 patients were eligible for inclusion in the PP data set. Forty-one patients were considered to have had severe disease at entry and received a more intense initial therapy regimen. The average age of patients enrolled was 54 years (52 years for tobramycin 0.3% [3 mg/mL] enhanced viscosity ophthalmic solution patients and 55 years for tobramycin 0.3% [3 mg/mL] ophthalmic solution patients) with a minimum age of 1 year and a maximum age of 91 years (both in the tobramycin 0.3% [3 mg/mL] enhanced viscosity ophthalmic solution group). A summary of patient demographics for all patients with conjunctival specimens collected on Day 1 is presented in Table I. There were no statistically significant differences between the distribution of patients receiving tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution and tobramycin 0.3% (3 mg/mL) ophthalmic solution for the baseline characteristics examined for this group or for the PP data set.

Efficacy

In the PP data set, 98% of the patients treated with tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution and 99% of the patients treated with tobramycin 0.3% (3 mg/mL) ophthalmic solution were categorized as having sustained cure/presumed eradication (Tab. II). There were no statistically significant differences between

TABLE VI - MOST FREQUENT OCULAR ADVERSE EVENTS JUDGED TO BE RELATED TO TREATMENT

Treatment	**Tobramycin 0.3% (3 mg/mL) enhanced viscosity solution (n=137)**		**Tobramycin 0.3% (3 mg/mL) solution (n=139)**	
Adverse event	**N**	**%**	**N**	**%**
Ocular pruritus	2	1.5	1	0.7
Ocular hyperemia	2	1.5		
Tearing	2	1.5		

the two treatments for the final clinical judgment at the test-of-cure visit (p=0.6037). Additionally, the confidence limits for the difference between treatments were well within the criterion of ±20% (-4.5% to 2.2%). There were also no statistically significant differences in the percentage of patients judged by the physicians to be cured/improved at any of the visits (Fig. 1) or for any of the other secondary outcome variables.

The PP data set did not take account of patients who failed to attend at all visits or who did not initially respond to treatment and took no account of the severity of the original presenting symptoms. No statistically significant difference in clinical cure rate was found between both treatment groups when either severe or non-severe subpopulations were compared or between severe and non-severe patients within the treatment groups (Tab. III).

Microbiological susceptibility testing

On Day 1 (pretherapy), conjunctival specimens were collected from 386 infected eyes of 274 patients. Bacteria were recovered from 340 (88.1%) of these specimens and 75 (19.4%) of the eyes had more than one organism recovered. A total of 422 isolates were recovered from the 386 Day 1 specimens; 344 of these (81.5%) were Gram-positive organisms, and 78 (18.5%) were Gram-negative. No fungi (mold or yeast) were isolated. A summary of organisms identified is given in Table IV. The spectrum of bacteria isolated from severe cases of conjunctivitis was similar to that for non-severe cases. The susceptibility to tobramycin determined for the major bacterial species identified is presented in Table V. Over 90% of strains of *Staphylococcus aureus* and 80% of strains of *Staphylococcus epidermidis* were susceptible to tobramycin. However, only 13% of *Haemophilus influenzae* and none of the strains of *Streptococcus pneumoniae* isolated were susceptible. In the PP data set only two strains of *S. epidermidis* were found to persist at the test-of-cure visit (one in each treatment group) and all strains of other bacteria isolated were eradicated. In fact, when all patients, with positive cultures on Day 1 who met the study inclusion criteria and received drug, were considered, there were only 18 patients classified as microbiological failures (7 in the tobramycin 0.3% [3 mg/mL] enhanced viscosity ophthalmic solution group and 11 in the tobramycin 0.3% [3 mg/mL] ophthalmic solution group). In four of these cases no organisms were isolated at the time of treatment failure and in five cases the original organism isolated was no longer found to be present. In only eight cases was persistence of the original infecting organism confirmed (two in the tobramycin 0.3% [3 mg/mL] enhanced viscosity ophthalmic solution group and six in the tobramycin 0.3% ophthalmic solution group). Eight of the patients considered as microbiological failures were exited from the study at the second visit, after only 2 to 3 days of treatment.

Safety

All 276 patients were evaluable for safety. No deaths or other serious adverse events were reported during the study. Reported adverse events were not serious, mainly mild to moderate in severity, and generally did not interrupt patient continuation in the study. Two adult patients, both receiving tobramycin enhanced viscosity ophthalmic solution, were discontinued from the study due to treatment related adverse events (each with symptoms of an ocular allergic reaction). Overall, 16 (5.8%) patients reported adverse events.

All adverse events judged to be treatment related are presented in Table VI. The most frequent ocular adverse events related to therapy with tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution were ocular pruritus (1.5%), ocular hyperemia (1.5%), and tearing (1.5%). All other ocular events occurred at an incidence of 0.7% (reported on only one occasion). The only ocular adverse event related to therapy reported with tobramycin 0.3% (3 mg/mL) ophthalmic solution was ocular pruritus (0.7%).

No clinically relevant, treatment related change in visual acuity or statistically significant difference between treatment groups was observed. Two changes in visual acuity occurred in the tobramycin 0.3% ophthalmic solution group.

DISCUSSION

It has been demonstrated that noncompliance is significantly higher when eyedrops are used more than twice daily, and that the mid-day instillation of a three times a day dosing regimen is the most likely to be omitted (15). In addition, noncompliance is known to correlate with many factors such as side effects of the medications, complexity of the therapeutic regimen, perceived severity of the disease, and lack of concern about health (16). Reduction of the dosage regimen for tobramycin in the treatment of acute

bacterial conjunctivitis from QID to BID should, therefore, be expected to provide advantages to patients. Indeed, in an earlier study BID dosing with an enhanced viscosity formulation of fusidic acid was demonstrated to improve compliance in younger patients (10). Intuitively, BID tobramycin 0.3% (3 mg/mL) ophthalmic solution is expected to demonstrate better compliance than the comparator since it is dosed twice a day rather than four times a day.

Aminoglycosides have a marked concentration-dependent bactericidal activity and a long post-antibiotic effect (PAE) (17-19). The PAE for tobramycin has been reported to extend for several hours with some species of bacteria (17). Clinical trials have also shown that greater bactericidal activity is achieved when higher concentrations of tobramycin are obtained (20) and that systemic once daily dosing with aminoglycosides is more efficacious than frequent dosing (21). In a pharmacokinetic study in healthy volunteers, it has been demonstrated that a much higher peak concentration of tobramycin is obtained in tears after administration of tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution than tobramycin 0.3% (3 mg/mL) ophthalmic solution (9). The concentration of tobramycin in tears also exceeded the MIC90 for ocular isolates (approximately 16 µg/mL) (22) for a longer period of time after administration of tobramycin 0.3% (3mg/mL) enhanced viscosity ophthalmic solution compared to tobramycin 0.3% (3mg/mL) ophthalmic solution. Mean duration of time over MIC90 in human tears was 44 minutes and 25 minutes for tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution and tobramycin 0.3% (3 mg/mL) ophthalmic solution, respectively (22). These considerations suggest that BID dosing with tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution should be an acceptable alternative for the treatment of acute bacterial conjunctivitis.

In this randomized clinical study, comparing tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution and tobramycin 0.3% (3 mg/mL) ophthalmic solution in acute bacterial conjunctivitis, both treatments were very effective, with 98% to 99% of patients, in the PP data set, categorized as having sustained cure/presumed eradication. There were also no statistically significant differences between the two treatments for the final clinical judgment, and for physician's impression at any of the study visits. No clinically significant differences were found in any of the ocular signs and symptoms assessed as secondary variables. Twenty-five tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution patients and 16 tobramycin 0.3% (3 mg/mL) ophthalmic solution patients out of the 274 patients included in the efficacy analyses (ITT) were rated as having severe disease at entry. In view of not disfavoring the tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution patients, all patients with severe infections received a four-times-a-day treatment during the first day. This can be considered as a shortcoming of the trial but the real aim was avoiding the risk of infradosing the tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution patients during their most symptomatic day (first day). Reported adverse events were typical of those previously observed with local ocular use of tobramycin (23). For both formulations they were not serious and generally resolved with or without treatment.

Tobramycin has been extensively used in the treatment of topical infections of the eye since it was originally introduced in the United States in 1981. However, susceptibility testing of conjunctivitis isolates from Europe and the Americas has indicated that two of the most common conjunctival pathogenic species, *H. influenzae* and *S. pneumoniae*, have not acquired resistance to the drug (24).

Significant levels of resistance have, however, been found among strains of *S. epidermidis* and *S. aureus* isolated from eyes of conjunctivitis patients. It is, therefore, not surprising that in this study several pretherapy isolates (pathogens cultured prior to tobramycin therapy) demonstrated tobramycin resistance. Nine percent of *S. aureus* strains and 20% of *S. epidermidis* strains isolated were classified as having acquired resistance to tobramycin (defined as MIC50 x 16). However, the majority of the bacterial pathogens were successfully eradicated in both tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution and tobramycin 0.3% (3 mg/mL) ophthalmic solution groups. In the PP data set only one bacterial strain in each treatment group was not eradicated by the treatment (both *S. epidermidis*).

This is expected since high local concentrations of antibiotic can be achieved in ophthalmic use. Pharmacokinetic studies have demonstrated that the new enhanced viscosity formulation delivers tobramycin to the ocular surface at a concentration generally much higher than the MIC of the most resistant bacterial isolates. Therefore, the possibility for tobramycin resistant bacteria surviving and proliferating is extremely low.

In conclusion, the results of this study indicate that tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution provides an alternative treatment for acute bacterial conjunctivitis that may help to improve patient compliance and satisfaction with therapy.

APPENDIX

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Dr. K. Kernt and the authors of the International TOBREX2X Group (Eu) have no proprietary interest.

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