EXTENDED REPORT

3-day treatment with azithromycin 1.5% eye drops versus 7-day treatment with tobramycin 0.3% for purulent bacterial conjunctivitis: multicentre, randomised and controlled trial in adults and children

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Aim: To compare the efficacy and safety of Azyter, azithromycin 1.5% eye drops, for 3 days with tobramycin 0.3% for 7 days to treat purulent bacterial conjunctivitis.

Methods: This was a multicentre, randomised, investigator-masked study including 1043 children and adults with purulent bacterial conjunctivitis. Patients received either azithromycin 1.5% twice-daily for 3 days or tobramycin 0.3%, 1 drop every two hours for 2 days, then four times daily for 5 days. Clinical signs were evaluated and cultures obtained at D0, D3 and D9 (where D refers to ''day''). Primary variable was the clinical cure at the Test-of-Cure (TOC)-visit (D9 $\pm$ 1), for patients with D0-positive cultures. The cure was defined as: bulbar conjunctival injection and discharge scores of 0.

Results: Among 471 patients with D0-positivity in the per protocol set, 87.8% of the azithromycin 1.5% group and 89.4% of the tobramycin group were clinically cured at the TOC-visit. Azithromycin was non-inferior to tobramycin for clinical and bacteriological cure. Clinical cure was significantly higher with azithromycin 1.5% at D3. The safety profile of azithromycin was satisfactory with a good patient and investigator's acceptability.

Conclusions: Azithromycin 1.5% for 3 days was as effective and as safe as tobramycin for 7 days. Furthermore, more azithromycin than tobramycin patients presented an early clinical cure at Day 3. Due to its twice daily dosing regimen for 3 days, azithromycin represents a step forward in the management of purulent bacterial conjunctivitis, especially in children.

Purulent bacterial conjunctivitis is characterised by muco-purulent discharge and conjunctival hyperaemia.[1] It is a contagious disease caused by one or more bacterial species that affects both sexes, all ages, ethnicities and countries. It may cause epidemics among people in close quarters, such as in nursery, school and student populations.[2 3]

Mild cases are generally considered to be self-limiting, resolving in 5 to 10 days. However, current consensus supports the use of topical antibiotics[4–6] as they (1) provide symptomatic relief, (2) hasten microbial remission[4 5] (3) shorten disease duration, (4) reduce risk of developing sight-threatening complications, (5) reduce rate of re-infection, (6) prevent infection spread. Recent meta-analysis[5 7] and a clinical trial[8] showed that antibiotics provide significantly better rates of early clinical remission, and both early and late microbiological remission than placebo.[5 6 9]

Most patients are treated empirically with topical antibiotics without previous bacteriological identification. Therefore, first-line treatment should offer the greatest potential for rapid elimination of the most commonly suspected pathogens together with a good safety profile. A new antibiotic with a low dosing frequency would be much more convenient for patients and, thus ensure better compliance thereby reducing the risk of selection of resistant bacteria.

Azithromycin is a second-generation macrolide that has rapid tissue distribution, sustained high tissue levels, uptake and transport by phagocytic cells.[10 11] A post-antibiotic effect has been demonstrated. These unique properties explain its efficacy when given only once or twice a day.[12] By oral route, its ocular bioavailability is good, since a single oral administration maintains prolonged azithromycin concentrations in tears and conjunctiva.[13]

This drug has a wide in vitro antimicrobial spectrum against gram-positive and gram-negative bacteria.[14 15] The bacterial strains most commonly found in acute conjunctivitis are gram-positive bacteria (*Staphylococcus epidermidis*, *S aureus*, *Streptococci* especially *Streptococcus pneumoniae*).[16] The most common gram-negative micro-organism is *Haemophilus influenzae*, also sensitive to azithromycin.[1 17 18]

The study objective was to compare the efficacy and safety of a 3-day treatment of azithromycin 1.5% in single-dose units with a 7-day treatment of tobramycin 0.3%,[19] in purulent bacterial conjunctivitis in adults and children.

METHODS

Study design

This was an international, multicentre, randomised, investigator-masked, parallel-group, non-inferiority trial. A double-blind design was not feasible because treatments differed in terms of dosage regimen (twice daily for 3 days vs every 2 h for 2 days, then four times daily for 5 days) and packaging (single dose vs multi-dose). Therefore, at each site, one investigator assessed ocular status in a masked fashion, while another investigator assessed safety and acceptability parameters.

Abbreviations: MITT, modified-intent-to-treat; TOC, test-of-cure

A total of 40 centres across eight countries (France, India, Bulgaria, Guinea Conakry, Morocco, Portugal, Romania, and Tunisia) actively recruited patients.

The study was conducted in accordance with Good Clinical Practice and all applicable guidelines, as well as the Declaration of Helsinki and local regulations. Local ethics committee approval was obtained prior to patient enrolment. Written informed consent was obtained from all participants (or from the parent/guardian for children).

Patients

The study population included adults, children, infants and newborns. Patients were eligible for inclusion if aged at least 1 day and diagnosed with purulent bacterial conjunctivitis defined as bulbar injection and purulent discharge.

Patients were excluded if presenting a history of (1) bacterial conjunctivitis diagnosed $\geqslant$7 days prior to inclusion, (2) bacterial infection due to trauma or foreign body, (3) dacryocystitis, (4) corneal ulceration or keratitis, (5) viral infection, (6) significant ocular abnormality, (7) amblyopia. Also excluded were: (1) contact lens wearers, (2) newborn not born at term, (3) patients having received systemic macrolides during the month before inclusion or topical treatments during the week before inclusion. Concomitant treatments such as systemic macrolides, other antibiotics, topical treatments, anti-inflammatory and/or immunosuppressives were forbidden.

Study medications and dosing regimen

Patients were randomised to receive:

- azithromycin 1.5% eye drops (Azyter, Laboratoires THEA), one drop twice daily for 3 days
- or tobramycin 0.3% eye drops (Tobrex, ALCON Laboratories), 1 drop every two hours up to 8 times a day for 2 days, then four times daily for 5 days.

Main outcome measures and procedures

At D0, D3 and D9, slit lamp examination and conjunctival sampling for bacterial analysis (except children $<$3 years old at D3) were performed.

Clinical efficacy assessments

Primary variable was clinical cure at the test-of-cure (TOC)-visit on D9$\pm$1 in the ''worse eye'' among patients with D0-positive cultures. Cure was defined as no bulbar injection and no discharge.

The investigator also assessed cure in the worse eye on D3 and in both eyes at each visit, and global efficacy.

Microbiological assessments

The Cagle's classification allows the differentiation between pathogenic bacteria from the normal eye flora, using validated thresholds based on colony counts. This classification is divided in 4 categories according to the pathogenicity level of bacteria. A bacteriological sample was considered positive if isolated bacteria were above the pathogenic thresholds published by Cagle for discrimination between non-pathological and pathological bacteria.[19–25]

Bacteriological resolution, defined as the absence or reduction below pathogenic threshold, was assessed at D3 and D9 for patients with D0-positivity.

Safety assessments

A safety evaluation was conducted for all included patients who received the study drug. Analysis was based on adverse events, symptoms upon instillation (burning/stinging/itching, stickiness, foreign body sensation, blurred vision), ocular signs, visual acuity and acceptability of treatment by both investigator and patient. For preverbal children, symptoms were assessed by the relatives.

Statistical analysis

In this non-inferiority trial, primary efficacy analysis was based on the per protocol set presenting D0-positivity. A separate modified-intent-to-treat (MITT) analysis was conducted in all randomised patients with D0-positivity. If both eyes were infected, the worse eye (or the right eye if equal severity) was chosen.

Evaluation was based upon a 2-sided 95% confidence interval (CI) on the difference in cure rate (azithromycin *minus* tobramycin). Azithromycin was considered non-inferior to tobramycin if the lower interval limit was not below -10%. Missing data were handled by using the last available assessment or by considering missing data as failure in case of treatment-related discontinuation. The enrolment target was set at 218 evaluable patients with D0-positivity per group. Sensitivity analyses using logistic regression were used to study prognostic factors, such as age, D0-causative organism, treatment and disease severity.

For safety, the Mann-Whitney test or Fisher's Exact test were used to compare treatments.

RESULTS

Patient disposition

Among the 1043 randomised patients [Intention-to-Treat (ITT)], 521 presented D0-positive cultures (MITT set). Among these 521 patients, 471 had no major deviation and were included in the per protocol set: that is, 245 patients for azithromycin, 226 for tobramycin. Only 3.7% of patients discontinued the study from D3 (fig 1).

Patient demographics and baseline characteristics

There were no between-group differences at baseline. The overall mean age $\pm$ SD was 39.0$\pm$20.7 years, ranging from 4 days old (newborn) to 87 years old. Among them, 150 patients (14.4%) were under 18 years old. There were 539 males (51.7%) and 504 females (48.3%).

Around 75% of patients presented moderate to severe purulent conjunctivitis. The percentage of D0-positive patients was 51.5% for azithromycin and 48.4% for tobramycin.

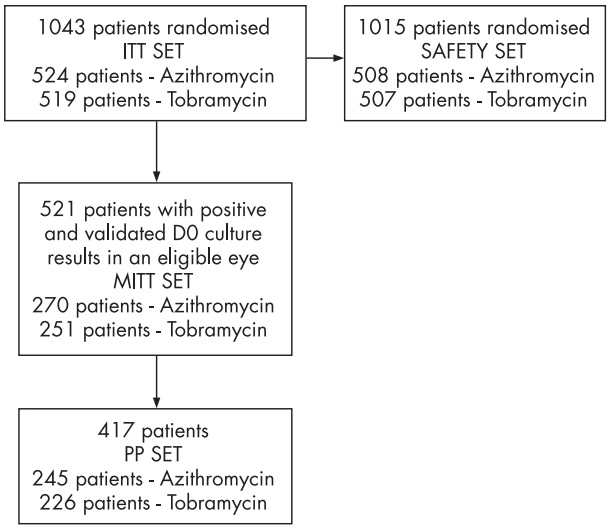

Figure 1 Flow-Chart of patient sets and protocol deviations.

The most frequent D0-bacteria were *S epidermidis* (39% of patients), followed by other coagulase-negative *Staphylococci* (23%), *S aureus* (18%), *Haemophilus* (7%), *S pneumoniae* (6%), *Enterobacteriaceae* (6%), and *Acinetobacter* (5%).

EFFICACY

Primary clinical efficacy

In the per protocol set, 87.8% of azithromycin-treated patients and 89.4% tobramycin-treated were cured on D9. Azithromycin 1.5% was non-inferior to tobramycin. The results were confirmed in the ITT and MITT sets (table 1).

Logistic regression analysis demonstrated no significant effect of any of the relevant prognostic factors: that is, treatment, D0-causative organism, age, disease severity.

Secondary clinical efficacy

Non-inferiority was found for all efficacy criteria at each assessment time. Additionally, azithromycin 1.5% was shown to have a statistically higher cure rate at D3 than tobramycin: 29.8% *versus* 18.6%. Therefore, azithromycin 1.5% could be considered as being superior to tobramycin at D3 since it showed more cases of earlier clinical cure.

Global efficacy assessment by the investigator was ''very satisfactory/satisfactory'' for more than 93% of patients in each group.

Bacteriological resolution

The rate of bacteriological resolution was 85.2% for azithromycin 1.5% *versus* 83.8% for tobramycin on D3, and 92.8% *versus* 94.6%, respectively on D9 (table 2). Azithromycin 1.5% was non-inferior to tobramycin at both time-points (table 2).

SAFETY

In the 1015 patients (508 azithromycin and 507 tobramycin) evaluable for safety assessment, no deaths or serious treatment-related adverse events were reported. Adverse events were mild to moderate. Only four patients presented treatment-related adverse events: three for azithromycin (two burning, one burning/foreign body sensation; two discontinued the study), and one patient for tobramycin (discharge).

The ocular surface safety profile of both studied products was satisfactory since no impairment was observed at the slit lamp examination. This good safety profile was supported by the investigator assessment of treatment acceptability on D3 based on the objective ocular signs. Treatment acceptability was rated satisfactory/very satisfactory in 91.7% of cases for azithromycin 1.5% and in 88.1% of cases for tobramycin. Upon instillation, some ocular symptoms were noted when azithromycin 1.5% was compared *versus* tobramycin. Despite these symptoms, the eye drops were rated as comfortable by 95% of patients in both groups on D9.

DISCUSSION

In purulent bacterial conjunctivitis, Azyter® is a new topical antibiotic eye drops offering the advantages of the pharmacodynamic/pharmacokinetic profile of azithromycin with a reduced dosing regimen and an appropriate activity spectrum. The ophthalmic packaging in single-dose units is particularly suitable to a context of infectious disease since it avoids the risks of contamination. The 6-administration treatment represents a major step forward for children and active people, allowing ease of use with one morning drop before the daily activities then an evening drop. Consequently, better compliance can be expected thereby reducing the risk of resistant-bacteria emergence.

To validate this 3-day concept in ophthalmology, a clinical program in healthy volunteers had explored pharmacokinetics of three azithromycin concentrations. The 1.5% concentration delivered BID for 3 days achieved azithromycin concentrations above the minimal inhibitory concentrations for 4 days in tears and for 7 days in conjunctiva. No safety issues were observed during five studies in healthy volunteers (unpublished data) and one study in more than 650 children presenting active trachoma (submission reference number: BJOPHTHALMOL/2006/099275).

The present study was designed to verify whether this reduced dosing regimen (BID for 3 days) could provide the efficacy required to treat purulent conjunctivitis with a good efficacy/safety profile. This non-inferiority study was well-powered and included a very large population of newborns, children, and adults. Tobramycin 0.3% was chosen as a reference antibiotic because it is recognised as an effective treatment for bacterial conjunctivitis in newborns, children and adults.[19 20 23–31] The tobramycin dosing regimen used (up to eight times daily for 2 days, then QID for 5 days) was the most commonly published.[19 20 23–31]

This study was designed to include adults as well as very young children (at least one day of age), for whom topical antibiotics are indicated. Patients were eligible if presenting both bulbar injection and discharge; both cardinal signs that are conventionally used in clinical trials.[8 32–34] Only patients with D0-positivity were included in the primary analysis set, thus reinforcing the diagnosis of purulent bacterial conjunctivitis. The observed rate of 50% microbiological D0-positivity was in accordance with the literature data.[23 27 31 34 35] At baseline, bacterial distribution was consistent with the published data.[8 25 27–29 36] Staphylococci were the most frequently isolated bacteria followed by *Haemophilus*, *Enterobacteriaceae*, *S pneumoniae* and *Acinetobacter*. In children under 12 years old, a higher prevalence of *Haemophilus* and *S pneumoniae* was reported.

Clinical cure at the TOC-visit on D9 was strictly defined: a score of 0 for both bulbar injection and purulent discharge. Therefore, improvement without complete clinical cure was a failure for the primary analysis. The TOC-visit was planned in accordance with the European guidelines, which recommend scheduling the TOC-visit between 3 and 10 days after the last dose of anti-infective treatment. This choice may have disadvantaged the azithromycin group whose TOC-visit took place 7 days after treatment completion compared to 3 days for the tobramycin group.

Both treatments were very effective. Clinical cure on D9 reported for 215 patients (88%) under azithromycin 1.5% and

Table 1 Primary efficacy variable–clinical cure in the worse eye on D9

	Number (%) of patients with bacteriological resolution in the worse eye (per protocol) set		Non-inferiority analysis (Azithromycin *minus* tobramycin)		
Set	**Azithromycin***	**Tobramycin†**	**Difference in cure rate**	**Exact 2 sided 95% CI on difference**	**Non-inferiority**
PP	215 (87.8)	202 (89.4)	−1.6%	(−7.5% to 4.4%)	Accepted
MITT	231 (85.6)	216 (86.1)	−0.5%	(−6.6% to 5.8%)	Accepted
ITT	447 (85.3)	440 (84.8)	0.5%	(−3.8% to 4.9%)	Accepted

*Azithromycin group: N = 245 PP, N = 270 MITT, N = 524 ITT; †Tobramycin group: N = 226 PP (per protocol), N = 251 MITT, N = 519 ITT.

Table 2 Bacteriological resolution in the worse eye on D3 and D9

	Number (%) of patients with bacteriological resolution in the worse eye (per protocol) set)		Non-inferiority analysis (Azithromycin minus Tobramycin)		
Time-point	Azithromycin* (n = 245)	Tobramycin† (n = 226)	Difference	Exact 2 sided 95% CI on difference	Non-inferiority‡
D3	202 (85.2)	181 (83.8)	1.4%	[−5.3% to 8.3%]	Accepted
D9	219 (92.8)	211 (94.6)	−1.8%	[−6.6% to 3.0%]	Accepted

*Azithromycin group: n = 237 at D3, n = 236 at D9; †Tobramycin group: n = 216 at D3, n = 223 at D9.
‡Based on non-inferiority margin of −10% defined for the primary efficacy variable.

202 patients (89%) under tobramycin, thereby demonstrating the efficacy of azithromycin 1.5%. The clinical cure rates observed were similar to the literature for complete resolution of the disease.[8 19 24 28 29 32 35–37]

Azithromycin 1.5% may provide a quicker resolution of the clinical signs than tobramycin. On D3, the clinical cure rate with azithromycin was significantly superior to that of tobramycin. This superior efficacy of azithromycin 1.5% at D3 may be explained by the sustained azithromycin concentrations above MIC in tears and conjunctiva.

Bacteriological resolution occurred rapidly in both groups, reaching 85% for azithromycin 1.5% *versus* 84% for tobramycin on D3, and 93% *versus* 95%, respectively on D9. Azithromycin 1.5% was non-inferior to tobramycin at both time-points. These bacteriological resolution rates were consistent with the rates usually reported.[8 19 21 23 24 28 29 31 32 34 37] Detailed microbiological analysis techniques and results will be published separately.

Azithromycin 1.5% was well-tolerated. No ocular surface impairment was observed at slit lamp examination. The eye drops were rated as comfortable by 95% of patients in both groups.

This study validates the expected advantages of the pharmacokinetic profile of azithromycin for ophthalmology. The results demonstrate the efficacy of the reduced dosing regimen of azithromycin 1.5% in treating purulent bacterial conjunctivitis.

Azithromycin 1.5% represents a major step forward in the management of bacterial conjunctivitis. It will be especially suitable for paediatric populations since its reduced dosing regimen partly resolves the issue of the repeated instillations of antibacterial eye drops in children.

CONCLUSION

Non-preserved ophthalmic solution of azithromycin 1.5% in single dose units has an innovative dosage regimen based on the pharmacokinetic results obtained in human studies: one drop BID for 3 days (unpublished data). The present study demonstrated that this treatment (6 instillations per eye) is highly effective in treating bacterial conjunctivitis in children and adults. It is non-inferior to tobramycin at D9 and superior to tobramycin at D3. It also presents a good safety profile.

Azithromycin 1.5% has the advantage of a shorter treatment duration and less frequent dosing than tobramycin 0.3% eye drops. This is expected to make instillation frequency more compatible with daily activities, improve treatment compliance, and limit patient premature treatment discontinuations, thereby reducing the risk of developing bacterial resistances. Azyter® eye drops can be expected to be a useful alternative therapy and a welcome addition to the Clinician's armamentarium for treating purulent bacterial conjunctivitis.

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