EXTENDED REPORT

Efficacy and safety of short duration azithromycin eye drops versus azithromycin single oral dose for the treatment of trachoma in children: a randomised, controlled, double-masked clinical trial

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Aims: Efficacy and safety of a short-duration treatment of azithromycin 1.5% eye drops versus oral azithromycin to treat active trachoma.

Methods: Randomised, controlled, double-masked, double-dummy, non-inferiority explanatory study including 670 children from Guinea Conakry and Pakistan if: 1–10 years old; active trachoma (TF+TI0 or TF+TI+ on simplified World Health Organisation (WHO) scale). Three groups received either: azithromycin 1.5% eye drops twice daily for 2 days, for 3 days or azithromycin single 20 mg/kg oral dose. Patients' contacts were treated whenever possible. Clinical evaluation was performed using a binocular loupe. Primary efficacy variable was the cure (no active trachoma (TF0)) at day 60. Non-inferiority margin for difference between cure rates was 10%.

Results: Cure rate in per protocol set was as follows: 93.0%, 96.3% and 96.6% in 2-day group 3-day group, and oral treatment group, respectively. Azithromycin 1.5% groups were non-inferior to oral azithromycin. The intend to treat (ITT) analysis supported the results. Clinical re-emergence rate was low: 4.2%. Ocular tolerance was similar for all groups. No treatment related adverse events were reported. Logistic regression analyses found prognostic factors such as: country ($p < 0.001$) and trachoma severity ($p = 0.003$).

Conclusions: In active trachoma, azithromycin eye drops twice daily for 2 or 3 days are as efficient as the WHO's reference treatment and represent an innovative alternative to oral azithromycin.

Trachoma is a keratoconjunctivitis caused by *Chlamydiae trachomatis*. If untreated, it may lead to trachomatous scarring, trichiasis and corneal opacity causing blindness in adults in contaminated areas. It is one of the most common causes of preventable blindness in the world, representing 3.6% of total blindness.^{1–7}

The traditional antibiotic strategy has been tetracycline 1% ointment, twice daily for six weeks or intermittently for six months.^{2–8–10} However, ointment is difficult to apply and compliance is poor.¹¹ The strategy more recently recommended by the WHO is a single oral dose of azithromycin (20 mg/kg in children or 1 g in adults) which has equal efficacy to several weeks of tetracycline.^{9–14} However, there is a risk that azithromycin initially planned for campaign against trachoma might be used to treat other systemic infections. Azithromycin could be diverted away from its initial target, children exposed to trachoma. Furthermore, the bacterial ecology of the strains responsible for systemic infections could be modified by inappropriate use of oral azithromycin.¹⁵ Therefore, a strong international demand has been expressed.¹⁶

Azithromycin 1.5% eye drops have been developed. Pharmacokinetic data in healthy volunteers suggest that twice daily ocular instillation for 2 or 3 days should be able to achieve the required conjunctival azithromycin levels to control trachomatous infection.

This randomised, controlled, double-masked, double-dummy, non-inferiority study compared the efficacy and safety of azithromycin 1.5% with a single oral dose of azithromycin for the treatment of active trachoma. This explanatory trial assessed the activity of these both anti-infective drugs on

episodes of infection in affected children, 2 months after treatment.

MATERIALS AND METHODS

Efficacy of this new medication on acute infection episodes was assessed by the percentage of clinical cure in children with clinically active trachoma, shortly after treatment (2 months). Therefore, efficacy was followed up on an individual basis. This design differs from pragmatic studies, which evaluate the long-term effect of strategies for the prevention of blinding trachoma at a community level.

OBJECTIVES AND HYPOTHESES

The objective was to assess the efficacy and safety of azithromycin 1.5% for 2 or 3 days, in comparison with oral azithromycin, for the treatment of active trachoma. The principal statistical hypothesis was that azithromycin 1.5% was non-inferior to oral azithromycin.

STUDY CENTRES AND ETHICAL CONSIDERATIONS

Patients were recruited from 21 villages in the Kankan area of Guinea Conakry and six villages in the Rawalpindi and Attock districts of Pakistan. The villages were endemic areas accessible and willing to participate.¹⁷ In the Guinean villages, we tried to

Abbreviations: GCP, good clinical practice; ITT, intend to treat; TF0, no active trachoma; (TF+TI0), trachomatous inflammation – follicular; (TF+TI), trachomatous inflammation – follicular and intense; WHO, World Health Organisation

screen all children. In the Pakistani villages, screening was done mainly in schools (primarily attended by boys).

The study is in accordance with the Declaration of Helsinki, "good clinical practice" (GCP), and applicable guidelines.^{18–20} Independent ethics committee approval was obtained in Guinea Conakry, Pakistan and France before the study. Written informed consent was obtained from each child's legally acceptable representative before any study-related procedures. The sponsor's monitors were present at every patient visit to verify adherence to GCP.

INCLUSION AND EXCLUSION CRITERIA

Active trachoma affecting mostly children, patients to be recruited were children.^{1 3 5 11} They could be enrolled if aged 1–10 years with trachomatous inflammation: TF+TI0 (trachomatous inflammation – follicular) or TF+TI+ (trachomatous inflammation – follicular and intense) on the simplified WHO grading system.²¹

The exclusion criteria were as follows: trichiasis or corneal opacity; fibrosis with palpebral deformation; ocular abnormality; ocular infection; organic amblyopia; hypersensitivity to the investigational product; immunosuppressive conditions; systemic steroids, or ophthalmic systemic antibiotics, or topical treatments, or systemic non-steroidal anti-inflammatory drugs prior to the study.

RANDOMISATION PROCEDURES AND TREATMENTS

Patients attended visits on days 0, 2, 30 and 60. On day 0, eligible patients were randomised to one of the three parallel groups: azithromycin 1.5% for 3 days or for 2 days, or azithromycin single oral dose. We used a double-dummy design with placebo eye drops and placebo paediatric suspension.

Azithromycin 1.5% (Azyter, manufactured under the supervision of Laboratoires Théa following the GCP) contained 1.5% azithromycin dihydrate in a preservative-free solution in single dose unit. One drop was instilled into each eye twice daily on days 0 and 1 (2-day group), or on days 0, 1, and 2 (3-day group). Oral azithromycin (Zithromax, Pfizer) was a paediatric suspension administered as a single 20 mg/kg oral dose on day 0.

The randomisation list used random permuted blocks of six (SAS V. 8.2). Within each village, patient numbers were allocated in ascending order using the next available number. Study drugs were identified by patient number using the randomisation list.

A member of the investigator's team administered the medications. Patients wore identification bracelets, and their height and weight were checked at each visit for identification purposes.

In order to limit the confounding factors for assessing the outcome of the initial trachoma episode, reinfection risks were strictly controlled. Persons coming to the investigation centre with the affected children were to be treated with oral azithromycin. Soap was provided and villagers were informed about well-known environmental risk factors for trachoma.^{1 3 6 9–11 22}

STUDY ASSESSMENTS

The ophthalmologists examined each eye under a 2.5× binocular magnifying loupe. Trachoma was graded according to the simplified WHO grading system.²¹

Tolerance and safety were assessed by a treatment acceptability assessment on day 2 and by adverse events recorded at each visit.

A conjunctival swabbing was taken on days 0, 30 and 60 under strictly sterile conditions and analyzed for *Chlamydia trachomatis* using a polymerase chain reaction.

STATISTICAL ANALYSES

The efficacy analysis was primarily assessed in the per-protocol set (patients with no major protocol deviations), and then verified in the intent-to-treat (ITT) set (patients with efficacy data) and total set (all randomised patients). Safety parameters were analysed in the safety set (all treated patients).

The primary endpoint was the cure at the end of the study, defined as a TF0 grade for trachoma (that is <5 follicles with at least 0.5 mm diameter in the upper tarsal conjunctiva) in the worse eye at study end (last observation carried forward if missing data).

Assessed on a one-sided 97.5% confidence interval on the difference in the cure rate (azithromycin 1.5% minus oral azithromycin), the non-inferiority was accepted if the lower interval limit was above –10%. The non-inferiority limit of 10% was chosen in accordance with studies of infectious diseases.^{23–27}

Since two dosing regimens were assessed, a sequential procedure was used: the 3-day regimen was firstly tested, and subsequently, 2-day treatment could be tested only if the 3-day treatment was already demonstrated as being non-inferior to oral azithromycin. This procedure ensured that the overall level of significance was 2.5%.

Based on this hypothesis (power of 80%) and a 10% rate of drop-outs, 200 evaluable patients had to be included per group.

Sensitivity analyses were performed in the per protocol set. Firstly, logistic regression was applied considering treatment and country. Then, logistic regressions were applied considering treatment, country and each of the following potentially prognostic factors: age, sex, household treatment, latrines, availability of water, face washing, animal pens, road access, contact with trachomatous persons and trachoma grade. Finally, combinations of factors were analysed using stepwise logistic regression (PROC CATMOD in SAS with model validation by PROC LOGISTIC).

The safety analysis was based on treatment-emergent adverse events.

RESULTS

Patient disposition

We performed this study from January to May 2004. In Guinea Conakry, we screened 7698 children and diagnosed 848 with active trachoma—that is, 11% prevalence (5%–23% across villages). In Pakistan, we screened 4300 children and diagnosed 120 with active trachoma that is, 2.8% prevalence (0%–16% across villages).

Overall 670 patients were randomised: 552 in Guinea and 118 in Pakistan (fig 1). Overall, 96% of randomised patients completed the study. No patient discontinued due to lack of efficacy and only one due to adverse event (unrelated). Over 99% of the ITT set received all planned doses of study medication.

Demography and baseline disease characteristics

Demography was similar in the three groups (table 1). Mean age was 4.7 years in Guinea and 7.0 years in Pakistan. Trachomatous grading was TF+TI0 for 518 patients (79.0%), TF+TI+ for 129 patients (19.7%) and TF0 for 9 patients (1.4%) (considered to be major deviations; table 2).

Efficacy results

Primary efficacy variable

In the total per protocol set, 95.2% of patients (541/568) had cure in the worse eye at month 2 (table 3). The cure rates were 93.0%, 96.3% and 96.6% in the 2-day, 3-day and oral treatment groups, respectively. Azithromycin 1.5% for 2 or 3 days was non-inferior to oral azithromycin in the per protocol set. The results were similar in the ITT set and in the total set.

Figure 1 Flow diagram of patient disposition, analysis sets, and protocol deviations. ^aSome patients had more than one major protocol deviation. ^bMost often allergic vernal keratoconjunctivitis characterised by papillae which could have been difficult to distinguish from follicles at the initial stages of the disease.

Logistic regression showed no significant treatment effect ($p = 0.158$) but a significant country effect ($p < 0.001$). For the other factors, both different logistic regression models showed a significant effect for trachomatous grading at baseline. Positivity to *Chlamydia* was not confirmed to be a prognostic factor by the stepwise logistic regression analysis. For mother treated with oral azithromycin, and animal pens, the logistic

regression models have a restricted validity, due to the sample size of some subgroups.

Predicted values for cure rate (%) derived from stepwise logistic regression model (table 4) showed that higher cure rates were observed in Guinea than in Pakistan ($p < 0.001$) and that patients with TF+TI0 at baseline had significantly higher cure rates than patients with TF+TI+ ($p = 0.003$).

Table 1 Summary of patient demography (ITT set)

Demographic variable	All patients ITT set (n = 656)	Treatment group		
		2-day eye drops (n = 222)	3-day eye drops (n = 220)	Oral azithromycin (n = 214)
males n (%)	327 (49.8)	103 (46.4)	120 (54.5)	104 (48.6)
females n (%)	329 (50.2)	119 (53.6)	100 (45.5)	110 (51.4)
Age (years): mean (SD)	5.07 (2.53)	5.06 (2.48)	5.21 (2.57)	4.93 (2.55)
Weight (kg): mean (SD)	18.09 (7.17)	17.67 (6.66)	18.44 (7.24)	18.16 (7.62)
Height (m): mean (SD)	1.07 (0.21)	1.07 (0.2)	1.08 (0.21)	1.07 (0.22)

Table 2 Trachomatous grading at baseline (ITT set)

Eye	Trachoma grade*	All patients ITT set (n = 656)	Treatment group		
			2-day eye drops (n = 222)	3-day eye drops (n = 220)	Oral azithromycin (n = 214)
Worse eye	TFO	9 (1.4)	5 (2.3)	1 (0.5)	3 (1.4)
	TF+TIO	518 (79.0)	171 (77.0)	173 (78.6)	174 (81.3)
	TF+TI+	129 (19.7)	46 (20.7)	46 (20.9)	37 (17.3)
Other Eye	TFO	95 (14.5)	29 (13.1)	23 (10.5)	43 (20.1)
	TF+TIO	463 (70.6)	158 (71.2)	158 (71.8)	147 (68.7)
	TF+TI+	98 (14.9)	35 (15.8)	39 (17.7)	24 (11.2)

TFO = no active trachoma (<5 follicles at least 0.5 mm in diameter in the upper tarsal conjunctiva); TF+TIO = trachomatous inflammation – follicular; TF+TI+ = trachomatous inflammation – follicular and intense.

*Simplified grading system.

Secondary efficacy variables

In the per protocol set, cure in both eyes was observed for 91.5%, 93.7% and 95.0% of patients. Azithromycin 1.5% for 2 or 3 days was non-inferior to oral azithromycin.

Only 4.2% of patients with cure at day 30 had clinical re-emergence of trachoma in either eye at day 60: 4.9%, 4.0%, and 3.6% in the 2-day, 3-day, and oral treatment groups, respectively. There were no significant differences between the groups with respect to trachoma re-emergence ($p > 0.545$).

All three treatments markedly reduced the trachomatous grading on days 30 and 60. There were no significant differences between the treatment groups with respect to trachomatous grading at either visit ($p > 0.170$).

Safety results

Ocular adverse events were reported in 10.8%, 8.9% and 13.1% of patients in the 2-day, 3-day and oral treatment groups, respectively. Systemic AEs events were reported in 2.6%, 10.2% and 9.0% of patients. None of the adverse events were treatment-related events. One patient (3-day group) had a serious unrelated adverse events (death due to head injury).

The most frequent unrelated ocular AE was an endemic tropical form of allergic vernal conjunctivitis occurring in 4–5% of patients in each group. There were no notable differences between the three groups.

Difficulty to instil eye drops was reported in 1–4% of patients in each group. Crying during instillation was reported in 7–8% of patients in each treatment group. There were no significant differences between the groups.

DISCUSSION

This explanatory study investigated the efficacy and safety of azithromycin 1.5% in the target population for which antibiotics are indicated for active trachoma. A targeted treatment study design^{10 12–14 16 28–30} (in which the percentage of cure of the initial episode was assessed with a strict control of the confounding factors in affected patients) was considered more relevant than a mass treatment study design^{31–36} (in which clinical and/or microbiological prevalence is assessed in pragmatic conditions in the whole populations). Indeed, the objective was to assess the efficacy of azithromycin eye drops for registration purposes. Therefore, it focussed on individual treatment of patients and it did not assess the prevention of blinding trachoma in a community. The study design was discussed with regulatory authorities before the initiation of the study. For the same reasons, a two-month follow-up was agreed to be adequate for the treatment of a disease episode.

The primary endpoint was cure at month 2, defined as a TFO grade.²¹ This is a validated and widely-used tool for the grading of trachoma used in most clinical trials.

Azithromycin 1.5% for 2 or 3 days was demonstrated to be non-inferior to oral azithromycin. The cure rates in our study were rather high. A review of randomised targeted treatment studies with oral azithromycin shows that clinical cure rates are very variable.^{10 12–14 16 28–30 33} Guzey *et al* reported a cure rate of 92% at month 3 following repeated doses of azithromycin (10 mg/kg for 3 days).²⁹ Bowman *et al* reported a cure rate of 88% at month 6 following a single dose (20 mg/kg).¹³ In a recent mass treatment study, West *et al* reported a cure rate of

Table 3 Primary efficacy variable: cure in the worse eye at the end of the study (per protocol set)

Observed values: number (%) of patients with cure in the worse eye (per protocol set)			
Cure in the worse eye at the end of the study	2-day eye drops (n = 199) (%)	3-day eye drops (n = 190) (%)	Oral azithromycin (n = 179) (%)
No	14 (7)	7 (3.7)	6 (3.4)
Yes	185 (93)	183 (96.3)	173 (96.6)
Confidence intervals and non-inferiority testing			
	Cure rate (%) exact 95% CI on cure rate	Difference in cure rate (%) exact 95% CI on difference	Non-inferiority of eye drops versus oral azithromycin
Treatment Group			
2-day eye drops	93 (88.5 to 96.1)		
3-day eye drops	96.3 (92.6 to 98.5)		
Oral azithromycin	96.6 (92.9 to 98.8)		
Comparisons between groups			
3-day eye drops minus oral azithromycin		–0.3 (–4.6% to 3.9%)	Accepted
2-day eye drops minus oral azithromycin		–3.7 (–8.6 to 1)	Accepted

Table 4 Stepwise logistic regression models - prognostic factors and predicted values for the cure rate (per protocol set)

Forward Stepwise Logistic Regression Model				
Treatment		p=0.164		
Country		p<0.001		
Trachomatous grading at day 0		p=0.003		
Predicted values for cure rate (%) derived from model				
Country	Trachomatous grading at day 0	2-day eye drops (n=199) n (%)	3-day eye drops (n=190) n (%)	Oral azithromycin (n=179) n (%)
Guinea	TF+TIO	127 (97.2)	115 (98.6)	119 (98.8)
	TF+TI+	36 (90.7)	40 (95.3)	26 (95.8)
Pakistan	TF+TIO	30 (84.3)	31 (91.8)	28 (92.6)
	TF+TI+	6 (60.5)	4 (76)	6 (77.9)

91% at month 2 in patients with low chlamydial loads at baseline.³⁶

This high cure rate in our study may be explained by the high compliance to treatment (over 99%) as all instillations were performed by the investigator's staff. In addition, the baseline prevalence in our study was lower than expected¹⁷ and than that reported in other studies.^{10 12-14 16 28-36} A low prevalence constitutes a factor for a better outcome and limits reinfection risks soon after episode resolution.

The cure rate 2 months after treatment is unlikely to be affected by the measures against reinfection. Indeed, in a recent Cochrane review, no beneficial effect of face washing alone or in combination with a treatment has been supported after a 6-month follow-up.³⁷ It is unclear whether a 12-month period is long enough to demonstrate its impact.³⁷ Similarly, giving families oral azithromycin is not susceptible to cure the affected children shortly after treatment. Those measures are essential for controlling one of the major confounding factors, that is, reinfection.

The participating countries were very different. In Pakistan, there were more boys and patients were older. It proved difficult to treat patients' contacts in Pakistan. This explains the statistically significant country effect, with lower cure rates in Pakistan than in Guinea.

The incidence of adverse events was low and no adverse events were treatment-related. However, the children were often too young for directed questioning about adverse events and, probably for cultural reasons, generally did not complain. Many trachoma studies did not report safety data, whilst others reported low incidences of adverse events.^{12 14 29 30}

In conclusion, this clinical trial showed that azithromycin 1.5% twice daily for 2 or 3 days has a similar efficacy to a single oral 20 mg/kg dose of azithromycin for the treatment of episodes of active trachoma in children 2 months after treatment.

Azithromycin 1.5% has several advantages compared to oral azithromycin. In particular, the risk of bacterial resistance should be substantially reduced. Therefore, azithromycin 1.5% may represent an innovative ophthalmic alternative to the WHO's reference treatment. The next step is to assess its effectiveness during pragmatic clinical trials in communities.

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