A Comparison of Oral Azithromycin with Topical Oxytetracycline/Polymyxin for the Treatment of Trachoma in Children

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Trachoma, an infectious keratoconjunctivitis caused by *Chlamydia trachomatis,* is a leading cause of preventable blindness in developing countries. In this study we compared oral azithromycin with oxytetracycline/polymyxin eye ointment (once daily for 5 days every 4 weeks; total of six treatment cycles) for the treatment of active endemic trachoma in 168 rural Egyptian children. A suspension of azithromycin was administered to children as a dose of 20 mg/kg by one of three schedules: a single dose, one dose a week for 3 weeks, and one dose every 4 weeks for a total of six doses. The children's clinical status and chlamydial infection rates were evaluated for 1 year. The clinical cure rates were 35% 2 months after initial treatment, 16% at 8 months (during the annual autumn epidemic of purulent conjunctivitis), and 47% at 1 year. The pretreatment chlamydial infection rate of 33% (determined by direct immunofluorescence) decreased to 5% at 2 months and was 9% at 12 months. There were no significant clinical or laboratory differences among the four treatment groups. Thus, 1–6 doses of azithromycin were equivalent to 30 days of topical oxytetracycline/polymyxin ointment and may offer an effective alternative means of controlling endemic trachoma.

Trachoma continues to be the leading cause of preventable blindness in the world. Although it has disappeared from industrialized countries, it is still endemic in sub-Saharan Africa, the Middle Eastern crescent, China, India, and other parts of Asia; trachoma is responsible for 15% of all blindness worldwide (i.e., 6 million persons are blind due to trachoma) [1]. Trachoma is a keratoconjunctivitis caused by *Chlamydia trachomatis,* usually serovars A, B, Ba, and C. Chronic conjunctivitis in early childhood produces conjunctival scarring leading to inturned eyelashes, corneal opacity, and blindness.

Intervention programs to prevent trachomatous blindness are now based on community-wide (mass) administration of topical antibiotics to the eyes of young children and surgical correction of inturned eyelashes in adults [2]. Although topical antibiotic treatment temporarily suppresses conjunctival inflammation and chlamydial eye infection, trachoma and chlamydial infection rapidly reappear in a large proportion of those treated [3, 4]. Moreover, chlamydial infection in trachoma is not limited to the eye but has been demonstrated in the nasopharynx and rectum in 6%–27% of children in communities with trachoma [5, 6]. Recurrent chlamydial infection of the eye may be caused by inadequate treatment, autoinoculation from the nasopharynx, or transfer from siblings or other sources.

Although several antimicrobial drugs have in vitro activity against *C. trachomatis,* only sulfonamides, tetracyclines, and erythromycin derivatives have been widely used in public health programs to control trachoma. Mass treatment with oral sulfonamides was abandoned by the early 1960s because of systemic complications [7]. Oral tetracyclines, particularly doxycycline, were effective in eliminating trachoma among Native Americans, among whom active disease was limited to older children and adolescents [8].

In a small study in Tunisia, oral doxycycline was also more effective than topical tetracycline for the treatment of trachoma in older children [9]. At present, trachoma has been controlled in most instances by administering topical tetracyclines (or, rarely, erythromycin ointment) daily for periods of 6–10 weeks or by intermittent dosing over a 6-month period [2]. Although oral doxycycline is effective and easy to deliver, it is contraindicated for use in children under 7 years old. Oral erythromycin requires frequent dosing, which is impractical in the control of endemic trachoma.

Azithromycin may offer an entirely new alternative for controlling trachoma [6]. It is active against *Chlamydia* species, localizes in peripheral cells, and has a half-life in tissue of 2–3 days after a single dose [10]. For genital *C. trachomatis*

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This study was approved by the University of California, San Francisco, Committee on Human Research (approval no. H438-10340) and by the Human Research Committee of the University of Alexandria (Alexandria, Egypt).

Oral informed consent was obtained from the parents of individual patients because of cultural and literacy constraints, and the guidelines for human experimentation of the U.S. Department of Health and Human Services were followed.

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infections, the Centers for Disease Control and Prevention recommends a single 1.0-g dose of oral azithromycin as an equivalent to 7 days of oral doxycycline therapy [11].

A trial of trachoma therapy in Gambia compared a single dose of azithromycin (20 mg/kg) in 97 subjects to twice daily topical tetracycline for 6 weeks in 97 subjects, 10 of whom also received oral erythromycin for 2 weeks for severe disease [6]. In that study, clinical signs of trachoma resolved at 6 months in 72% of subjects who were treated with oral azithromycin and in 76% of those who were treated with tetracycline ointment. There was no difference between the two treatment groups at 4, 8, 16, and 26 weeks after treatment. Chlamydial antigen in eye or nasal swabs decreased from 60% pretreatment to <10% at 4 weeks after treatment and then rose to 40% at 26 weeks. In this Gambian study, a single dose of azithromycin was as effective as 84 doses of topical tetracycline in suppressing clinical disease and reducing chlamydial infection.

In the pilot study described herein, we compared three dosage schedules of oral azithromycin with topical oxytetracycline/polymyxin for treating children with trachoma in two rural villages in northern Egypt that have endemic severe disease that results in blindness [12]. The purpose of this trial was to evaluate several dosage regimens of oral azithromycin for the treatment of children with active trachoma. This study of different dosages of oral azithromycin was intended as a pilot trial for a larger study of community-wide azithromycin treatment.

This clinical trial was double-masked, placebo-controlled, and randomized. One group of children with active inflammatory trachoma received topical oxytetracycline/polymyxin eye ointment according to a World Health Organization (WHO)-recommended intermittent schedule for 6 treatment cycles; three other groups of children received either a single dose of oral azithromycin (20 mg/kg of body weight), one azithromycin dose once weekly for a total of three doses, or one azithromycin dose once every 4 weeks for a total of six treatments. Trachoma was evaluated before treatment and at intervals during and after treatment for 1 year by clinical examination and by direct fluorescent antibody staining (MicroTrak, Syva, Palo Alto, CA) of conjunctival smears.

Patients and Methods

Experimental design. To evaluate the treatment of trachoma with oral azithromycin vs. with topical tetracycline ointment (the currently recommended treatment), children in two villages in northern Egypt were screened clinically for active trachoma in February 1992. Children in two rural villages in Beheira Governorate in northern Egypt who were older than 2 years of age and up to 10 years of age were screened clinically for active inflammatory trachoma. A total of 168 children were randomized to one of the four treatment groups in blocks of eight. Children participated in the study with the consent of their families. Children were examined at intervals for 1 year after administration of the four treatment regimens.

Medications. A combination of 1% oxytetracycline and polymyxin (10,000 units/g) ointment was provided by Pfizer Egypt. This is the only form of ophthalmic tetracycline available in Egypt. Ointment was applied by trained medical personnel at a central location in each village. A suspension of azithromycin (200 mg/5 mL) for children and an identical-tasting placebo suspension were provided by Pfizer International. Each child was weighed, and an appropriate measured dose of drug or placebo suspension was transferred to a paper cup; each child then drank the contents of the paper cup. A treatment record card was kept for each child.

Children were randomized by blocks to one of the four treatment schedules: (1) Topical oxytetracycline/polymyxin ophthalmic ointment once daily for 5 consecutive days every 28 days for a total of six 5-day periods plus oral placebo suspension (n = 43); (2) A single dose of azithromycin suspension (20 mg/kg of body weight) (n = 40); (3) Azithromycin suspension (20 mg/kg once weekly for 3 consecutive weeks (n = 43); or (4) Azithromycin suspension (20 mg/kg) once every 28 days for a total of six treatments (n = 42).

At the time that each dose of azithromycin was administered, children who were not receiving the oral antibiotic were given an identical dose of an oral placebo suspension, which consisted of the suspension that did not contain azithromycin. A placebo ophthalmic ointment was *not* used in this trial. The schedule of treatments was as follows:

16 February 1992: Eye ointment (one group) or azithromycin suspension dose (three groups) (single azithromycin dose completed)
24 February 1992: Azithromycin (one group) or placebo suspension (three groups)
2 March 1992: Azithromycin (one group) or placebo suspension (three groups) (three azithromycin doses completed)
16 March 1992: Eye ointment and placebo suspension (one group) or azithromycin (one group) or placebo suspension (two groups)
13 April 1992: Eye ointment and placebo suspension (one group) or azithromycin (one group) or placebo suspension (two groups)
14 May 1992: Eye ointment and placebo suspension (one group) or azithromycin (one group) or placebo suspension (two groups)
7 June 1992: Eye ointment and placebo suspension (one group) or azithromycin (one group) or placebo suspension (two groups)
5 July 1992: Eye ointment and placebo suspension (one group) or azithromycin (one group) or placebo suspension (two groups) (six azithromycin or topical oxytetracycline/polymyxin treatment cycles completed)

Clinical evaluation. Patients were clinically examined for

Table 1. Clinical evaluation of trachoma.

TT: Inturned eyelashes (trichiasis or entropion) due to trachomatous conjunctival scarring [13]
TF: Five or more conjunctival follicles on the central tarsal surface of the everted upper lid [13]
TI: Trachomatous infiltration of the upper tarsal conjunctiva that obscures at least 50% of the deep underlying blood vessels [13]
TS: Trachomatous scarring of the conjunctiva
0 = No evidence of trachomatous scarring
1 = Small trachomatous scars anywhere on the conjunctiva
2 = Scarring involving most of the upper tarsal conjunctiva
3 = Diffuse tarsal scarring producing distortion or shortening of the upper lid with inturned lid margin
CO: Corneal scars
0 = None
1 = Peripheral scar, no central corneal opacity
2 = Nebular scar in central cornea, but pupillary margin easily seen
3 = Central scar obscuring pupillary margin
Trachoma status
0 = No signs of trachoma
1 = Active inflammatory trachoma
2 = No trachoma activity (inflammation) but significant signs of trachoma (conjunctival scars or Herbert's pits)

signs of trachoma by observing the external eye with the aid of a 2.5× binocular loupe and a handheld flashlight. The clinical findings were recorded with use of a modified form of the WHO recommendations for the simplified diagnosis of trachoma [13]. The major modification of this simplified description was the use of a more-detailed grading of conjunctival scarring based on an earlier WHO scoring system [2]. The status of each eye was defined as follows: no signs of trachoma; active inflammatory trachoma; or cicatricial signs of trachoma (typical conjunctival scars or Herbert's pits) but no conjunctival follicles or papillary infiltration. These signs are summarized in table 1. Ophthalmologists experienced in the diagnosis of trachoma performed all examinations and were masked as to the treatment used. At least two ophthalmologists examined each child at each examination.

Laboratory test. Conjunctival specimens for smears were taken at each examination with a calcium alginate swab, and the material was transferred to a premarked circle of 1 cm on a glass slide and air-dried. The slides were fixed with methanol, were stored, and were transported to San Francisco at ambient temperatures. Batches of slides were stained by direct fluorescent antibody, with positive and negative control slides in each batch. Experienced technicians examined each slide for chlamydial elementary bodies; the number of elementary bodies was counted on each slide and was recorded as "up to 200" or as ">200" [14].

Schedule of examinations. Examinations were done on 12 February 1992 (pretreatment), 12 April 1992 (2 months), 4 July 1992 (before the last treatment of the monthly azithromycin and ointment groups; 5 months), 15 October 1992 (8 months), and 22 February 1993 (12 months). The examinations covered a full calendar year to account for the annual variations in purulent conjunctivitis, which increases in prevalence in the late spring and summer and reaches epidemic levels in late autumn [7].

Results

Trial participants. Of the 168 children in the trial, 111 (66%) were 2–5 years of age and 57 (34%) were 6–10 years of age (table 2). Although case selection was not population based, this age distribution of active cases was similar to that noted in our previous studies in Egypt. This group does not include three children whose family did not want them to participate in the study; another child was excluded because there was no record of the initial examination. In most cases, children were lost to follow-up at specific examinations because they and their family were not in the village or because the child could not be found on the day of the examination.

Clinical outcome. In this trial, only children with active inflammatory trachoma were selected for treatment. The number of children who did not have clinically active trachoma is summarized in table 3. The data at 2 months and 5 months were obtained immediately before administration of the third and sixth azithromycin doses that were given every 4 weeks (total of six doses). At 2 months, trachoma was clinically resolved in 17 children in the group receiving azithromycin in three weekly doses and in only 11 children in the group receiving a single azithromycin dose (table 2); however, these differences are not statistically significant ($P > .5$). Cure rates had declined by October, during the peak of the annual epidemic of purulent conjunctivitis.

By 1 year after treatment (February 1993), however, the overall cure rates were roughly equivalent at 47% overall. The clinical responses showed no statistically significant differences between treatments and did not appear to be affected by age

Table 2. Age and sex of 168 Egyptian children treated for trachoma.

Age group (y)	Female	Male	Total
2	9	19	28
3	10	14	24
4	11	16	27
5	17	15	32
6	5	7	12
7	4	13	17
8	5	6	11
9	4	4	8
10+	3	6	9
Total (%)	68 (40.5)	100 (59.5)	168 (100)
No. of children aged 1–5 years/total no. of children (%)	47/68 (69.1)	64/100 (64.0)	111/168 (66.1)
No. of children aged 6–10 years/total no. of children (%)	21/68 (30.9)	36/100 (36.0)	57/168 (33.9)

Table 3. Number of children whose trachoma was not active after treatment with tetracycline ointment or oral azithromycin.

Variable	Date				
	2/92	4/92	7/92	10/92	2/93
No. of months after first dose	0	2	5	8	12
Treatment					
Oxytetracycline/polymyxin eye ointment	0/43	14/42 (33)	10/40 (25)	4/39 (10)	18/42 (43)
Azithromycin (1 dose of 20 mg/kg)	0/40	11/39 (28)	9/38 (24)	7/37 (19)	20/39 (51)
Azithromycin (1 dose per week for 3 weeks)	0/43	17/40 (43)	13/39 (33)	6/34 (18)	22/39 (56)
Azithromycin (1 dose every 4 weeks for a total of 6 doses)	0/42	14/39 (36)	11/40 (28)	7/40 (18)	15/39 (38)
Total no. of children with clinically inactive trachoma/total no. of children examined (%)	0/168	56/160 (35)	43/157 (27)	24/150 (16)	75/159 (47)

NOTE. All values represent the no. of children with clinically inactive trachoma/no. of children examined (%).

or initial severity of inflammatory disease ($P = 2.34$ by Cox's proportional hazards model comparing each azithromycin dosage group with the oxytetracycline/polymyxin group).

The clinical evaluation of trachoma used in this study identified severely inflamed eyes, moderately inflamed eyes, and eyes with no trachomatous inflammation. Previous studies have shown that patients with severely inflamed eyes have a significantly higher risk of developing potentially blinding complications later in life (e.g., inturned eyelashes) [14]. From 35% to 50% of children in each group had severe disease before treatment was administered (figure 1). This was reduced substantially in all groups at 2 and 5 months and rose somewhat at 8 months (October 1992), during the annual epidemic of purulent conjunctivitis, then declined to ~15% by 1 year (February 1993) in all groups (figure 1). Thus, the prevalence of potentially blinding trachoma was not significantly different in these children at 1 year regardless of the treatment group.

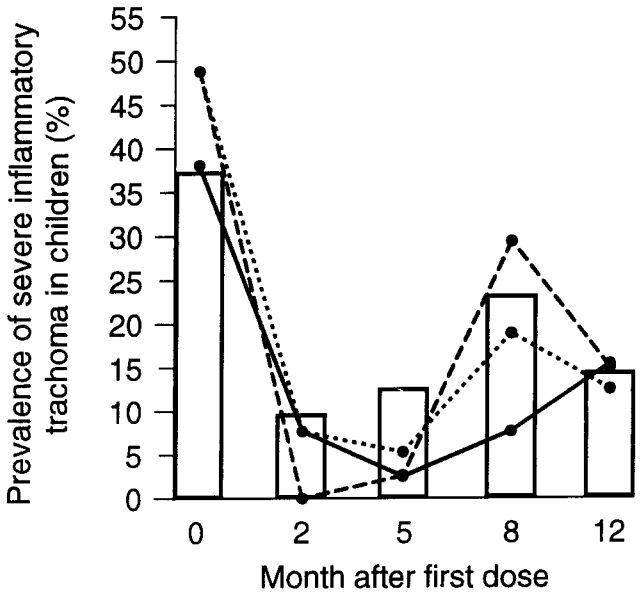

Figure 1. Prevalence of severe inflammatory trachoma in Egyptian children after treatment with topical oxytetracycline/polymyxin or oral azithromycin. Open bar = topical oxytetracycline/polymyxin ointment (once daily for 5 consecutive days every 4 weeks for a total of 6 cycles); dotted line = one dose of azithromycin (20 mg/kg); dashed line = one dose of azithromycin once weekly for a total of 3 doses; solid line = one dose of azithromycin every 4 weeks for a total of 6 doses. There is a decrease in severe trachoma at 2 months after treatment in all groups. The anomalous increase in severe disease at 8 months corresponds to the annual epidemic of purulent conjunctivitis (October 1992). Following this autumn epidemic, the rates of severe disease decrease again at 12 months (February 1993).

Conjunctival chlamydial infection. The number of conjunctival smears with two or more *C. trachomatis* elementary bodies per smear and those with 10 or more elementary bodies per smear is presented in table 4 for all children. Before treatment, the overall rates of chlamydial infection were 33% among children with clinically active trachoma, with 24% having 10 or more elementary bodies. At 2 and 5 months after start of treatment the rates of infection had decreased to ≤5%. In October 1992 (8 months) the rate was 13%, and in February 1993 (12 months) it was 9.4%. This finding reflects previous experience that the rate of chlamydial infection that is determined by laboratory tests for trachoma declines after chemotherapy to a greater extent than the clinical disease [3, 4].

Discussion

In communities with blinding endemic trachoma, such as those in Egypt that we studied, eye infection due to *C. trachomatis* in early childhood is probably universal; one small study in Egypt showed that 75% of children develop some laboratory evidence of chlamydial exposure by 1 year of age. *C. trachomatis* eye infections may be inapparent, and reinfection is also highly likely, particularly among younger children [15]. Annual epidemics of purulent conjunctivitis occur each autumn; they are spread by transfer of eye discharges by eye-seeking flies and are caused by pathogenic organisms

Table 4. Number of conjunctival smears with chlamydial elementary bodies for children with trachoma who were examined between February 1992 and February 1993.

Variable	Date of examination				
	2/92	4/92	7/92	10/92	2/93
No. of months after first dose	...*	2	5	8	12
Treatment					
Oxytetracycline/polymyxin eye ointment (5 days every 4 weeks × 6 cycles)	12/40 (8)	3/41 (1)	2/37 (1)	6/39 (3)	5/33 (4)
Azithromycin (one dose)	11/42 (10)	1/41 (0)	1/38 (1)	4/37 (2)	2/36 (1)
Azithromycin (once weekly for 3 weeks)	19/38 (13)	1/41 (0)	3/38 (1)	6/34 (3)	2/34 (2)
Azithromycin (once every 4 weeks for a total of 6 doses)	11/40 (8)	3/37 (0)	0/32 (0)	3/37 (1)	4/35 (2)
Total no. of smears with ≥2 EB/total no. of smears (%) [total no. of smears with ≥10 EB]	53/160 (33) [39]	8/160 (5) [1]	6/145 (4) [3]	19/147 (13) [9]	13/138 (9) [10]

NOTE. EB = elementary bodies. All values except for the totals represent the no. of smears with ≥2 elementary bodies/total no. of smears (no. of smears with ≥10 elementary bodies).

* The first treatment was given on 16 February 1992.

(*Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae* biogroup *aegyptius,* and occasionally a gonococcus-like *Neisseria* species, *N. kochii*) [7, 16]. The spread of *C. trachomatis* is probably also enhanced during this period. Because trachoma is a chronic disease, treatment must be evaluated at 1 year to allow for the effect of the autumn epidemics of purulent conjunctivitis.

This clinical trial was designed to compare three dosage schedules of oral azithromycin with the intermittent topical tetracycline treatment recommended by WHO [2]. Although initially effective, both clinical disease and chlamydial eye infection appeared again after treatment in all treatment groups. Nevertheless, at the end of 1 year, the prevalence of disease (particularly of severe, potentially blinding trachoma) and of chlamydial eye infection was reduced substantially in all four groups. It is likely, then, that children were reinfected by untreated family members and other individuals. Indeed, by October 1992 (8 months), during the annual epidemic of purulent conjunctivitis, the chlamydial infection rate had risen in all groups.

To reduce the problem of reinfection, WHO recommendations for the treatment of endemic trachoma (defined as 20% or more active disease among children in a community) are based on community-wide (''mass'') therapy [2]. This practice was established with the use of oral sulfonamides for trachoma in the late 1930s and continued when topical tetracyclines or erythromycin eye ointments were substituted in the 1950s (mainly to avoid the high complication rates with oral sulfonamides) [7].

In contrast with treatment of individuals with active trachoma, community-wide therapy with oral azithromycin should decrease chlamydial rates in the whole community and thus decrease new and repeated infections in addition to having a therapeutic effect on the active disease. Even if a single dose or three weekly doses are only equivalent to the intermittent topical tetracycline treatment, azithromycin has a clear advantage (noted by field personnel in this study) in ease of administration. In practice, both children and adults object to repeated doses of eye ointment that are uncomfortable and blur vision, so compliance to treatment schedules is often inadequate. Moreover, the ointment is difficult to deliver and usually requires trained personnel for effective application.

Although the suspension of azithromycin for children also requires trained personnel, the time to deliver 1–3 doses is considerably less than the 30–60 days of family or school visits required for ointment treatment. In this trial, azithromycin was well tolerated and only two children (of 125 treated) complained of nausea. To evaluate the full potential of azithromycin for the control of blinding trachoma, treatment trials will need to compare oral azithromycin to standard treatment in whole communities.

Although azithromycin is relatively expensive in developed countries, the cost of the drug in some developing countries is much lower and may change over time. However, in judging the cost of treatment, particularly mass treatment with this drug, the total cost of drug delivery and compliance with the application of topical antibiotic ointments must be used for comparison. Community-wide treatment with ointment requires a well-organized program with highly motivated field personnel. In practice, older children and adults are resistant to taking the ointment. Thus, there are substantial costs attached to the alternative treatment (30–60 days of topical tetracycline). It is clear that community-wide treatment with oral azithromycin should be evaluated as a central strategy for endemic blinding trachoma.

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