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Three-Day Course of Oral Azithromycin vs Topical Oxytetracycline/ Polymyxin in Treatment of Active Endemic Trachoma

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Purpose: The aim of this study on endemic trachoma was to carry out a comparison of azithromycin (3-day course, oral dose of 10 mg/kg per day) with conventional treatment (topical oxytetracycline/polymyxin ointment; twice a day for 2 months) in a rural area near Sanliurfa, Turkey.

Methods: Ninety-six subjects with active trachoma were randomly assigned conventional or azithromycin treatment. Subjects were examined 1, 2, 3, and 6 months after the start of treatment. Clinical findings were recorded for each eye. Swabs were taken from upper eyelids 3 and 6 months after the start of treatment for direct fluorescein antibody test.

Results: By six-month follow-up, trachoma had resolved clinically in 43 (89.58%) of the 48 subjects who received azithromycin, compared with 33 (68.75%) of the 48 who were treated conventionally. Microbiological success rates (direct fluorescein antibody test negativity) were 83.33% in the azithromycin group and 62.50% in the conventional therapy group. Compliance with both treatments was good. By 6 months, 14.58% of the subjects in azithromycin group and 33.33% of the subjects in the topical treatment group were reinfected. There were significant differences in the efficacy of the treatment effects and the re-emergence of disease between the two treatment groups. Azithromycin was well-tolerated.

Conclusions: These results indicate that azithromycin may be an effective alternative for patients with active trachoma. As a systemic treatment, a 3-day course oral dose has important potential for trachoma control. **Jpn J Ophthalmol 2000;44:387–391** © 2000 Japanese Ophthalmological Society

Key Words: Azithromycin, oxytetracycline/polymyxin, trachoma.

Introduction

Trachoma, an ocular infection caused by *Chlamydia trachomatis*, is the second leading cause of blindness worldwide. Active trachoma occurs predominantly in children in hyperendemic communities, with the risk of blinding complications occurring in middle-aged and older adults.[1,2] Although trachoma has been controlled in some areas, predictions based on demographic trends suggest that the burden of both infection and blindness is likely to increase.[3] There is a need for effective intervention to control ocular *Chlamydia trachomatis* infections.

The currently recommended treatment of trachoma is topical tetracycline eye ointment for at least 6 weeks, or on 5 consecutive days a month for 6 months.[4] It is suggested that subjects with a severe form of the disease should, in some circumstances, receive systemic therapy. There is a wide spectrum of opinion among trachoma experts about the effectiveness of these recommendations, reflecting a scarcity of data from controlled trials in endemic areas on which rational decisions about therapy can be based.[5,6]

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There are several reasons why this treatment is less than satisfactory. It is difficult to apply ointment to the eyes of young children. The ointment can cause discomfort or blurring of vision and melts under conditions of high ambient temperature. Many infected children have no symptoms and even in circumstances where ointment is given free it can be difficult to motivate parents to continue treatment for the stipulated period. A systemic treatment effective in a short period would thus represent a substantial advance in the chemotherapy of active trachoma.

Azithromycin is a recently approved azalide antibiotic with the molecular formula of $C_{38}H_{72}N_2O_{12}$, and a molecular weight of 749.00. It is a derivative of erythromycin, containing an extra methyl-substituted nitrogen at position 9a in the lactone ring (Figure 1). This modification confers good bioavailability, with sustained high tissue concentrations after an oral dose. Azithromycin achieves high concentrations in phagocytic cells and in fibroblasts. It appears that fibroblasts serve as a reservoir of azithromycin in tissues, allowing activity against organisms and possibly transferring the antibiotic to phagocytic cells for activity against intracellular pathogens and delivery to infection sites.[7] The high macrophage and tissue concentration of the drug and prolonged half-life suggest that azithromycin could potentially be used in shorter treatment regimens.[8,9] The present study compared the clinical and microbiological efficacy and safety of a 3-day course of azithromycin with a conventional 8-week course of topical oxytetracycline/polymyxin for the treatment of young patients with active ocular *Chlamydia trachomatis* infection.

Materials and Methods

In April 1998, an ocular survey was done in four villages of Sanliurfa by a trained observer (MG). The everted upper lids of both eyes were examined with a binocular magnifying loupe. Findings were graded according to the simplified World Health Organization grading system.[10] Ninety-six subjects with bilateral active trachoma or showing the symptoms given below were selected. The existence of an active trachoma was clinically characterized by the presence of at least 5 follicles associated with a papillary hypertrophy of the upper tarsal conjunctiva and microbiologically characterized by the presence of at least 5 elementary bodies per direct fluorescein antibody test slide. Clinical signs and symptoms taken into consideration were follicular conjunctivitis and papillary hypertrophy of the upper tarsal conjunctiva with discharge, redness, irritation and burning-stinging sensation and eyelid swelling.

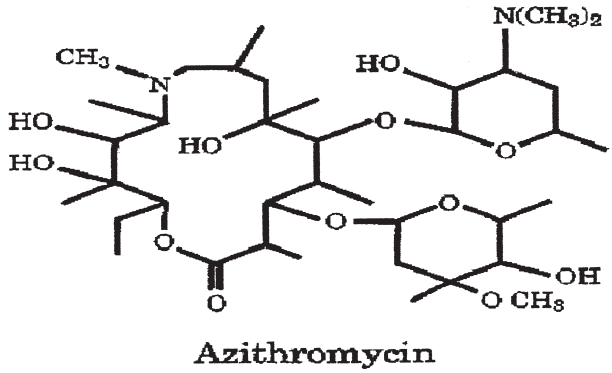

Figure 1. Chemical structure of azithromycin.

Ninety-six patients were randomly assigned conventional or azithromycin treatment. Randomization was by room, all active cases within a room receiving the same treatment. Baseline eye swabs were taken from all patients before treatment.

Expected effects, side effects, advantages, and disadvantages of both treatment methods were explained to patients who participated in the study and/or their parents, and informed consent was obtained.

Azithromycin suspension (200 mg/5 mL, Zitromax; Pfizer, Istanbul, Turkey) administered as a 3-day course (10 mg/kg per day) by mouth; a syringe was used for measurement and administration. Subjects randomized for conventional treatment were administered 0.5% oxytetracycline HCl/polymyxin eye ointment (Terramycin, 5 mg/g oxytetracycline HCl, 1 mg/g/polymyxin B sulfate; Pfizer) to each eye twice daily for 8 weeks.

Possible side effects were investigated in both groups by means of a standard interview, 7 days after treatment started. The interview protocol contained both specific questions about gastrointestinal symptoms in the preceding 7 days and open questions about the general health of the subjects. At subsequent follow-up, mothers were questioned about the general health of the subjects and any adverse events recorded.

The following laboratory tests for safety evaluation were obtained at baseline and at weeks 2 and 4: complete blood count with differential and platelet counts, prothrombin time, activated partial thromboplastin time, gamma glutamyl transferase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum bilirubin, lactate dehydro-

genase, blood urea nitrogen, serum creatinine, serum calcium and phosphorus, electrolytes, total protein, albumin, blood glucose, uric acid, serum cholesterol, and urinalysis.

Conventional treatment was applied by the patients' mothers, supervised by a trained nurse. Compliance with conventional treatment was assessed by a system of witnessed treatments; the subject's name was written on a form each time a treatment was witnessed. More than 95% of scheduled treatments were witnessed.

Subjects were examined 1, 2, 3, and 6 months after the start of treatment. Clinical findings were recorded for each eye. Swabs were taken from upper eyelids 3 and 6 months after the start of treatment. A dacron swab was rubbed on the everted upper tarsal conjunctiva, after which it was rolled on a slide for the direct antibody immunofluorescence test. Methanol-fixed slides were stained with monoclonal-fluorescein isothiocyanate antibody conjugate to the major outer membrane protein. Smears were considered positive if 5 or more elementary bodies per slide were seen.[11]

Noticeable symptomatic relief and considerable resolution of clinical signs (disappearance of papillary hypertrophy, decrease in the number and size of follicles) were considered as clinical success, and a negative direct fluorescein antibody test was accepted as microbiological success.

In cases where this test was negative in the third month, a positive test result obtained in the sixth month was considered as the establishment of a reinfection, whether a noticeable re-appearance of clinical signs and symptoms was present or not. For statistical analysis of the results, the chi-square test was used to compare the treatment groups.

Results

There were 96 subjects aged from 2 to 18 years (Table 1). The treatment groups did not differ significantly in age or sex distribution.

Symptoms of diarrhea, vomiting, and abdominal pain occurred in the azithromycin group (Table 2). There were no serious adverse reactions and both treatments were well-tolerated. No abnormalities were determined in the laboratory test results. All symptoms resolved spontaneously and none required treatment. Compliance with conventional treatment was extremely good. Local adverse reactions were not seen in the conventional therapy group.

At 3 months, the clinical signs of 44 (91.67%) subjects in the azithromycin group and the clinical signs of 36 (75.00%) subjects in the conventional treatment group had resolved (P = .029). These rates were 89.58% and 68.75% at 6 months, respectively (P = .012) (Table 3). The rate of reinfection by 6 months was 33.33% in the conventional treatment group, as opposed to 14.58% in the azithromycin group, and the difference was statistically significant (P = .027). Antigen positivity at baseline and severe or moderate disease were associated with persistence of clinical signs, and there was a tendency for younger patients to have more persistent clinical signs.

There were significant differences in the prevalence of direct fluorescein antibody test positivity in ocular swabs between the therapy modalities (Table 4).

Table 1. Baseline Comparisons of Treatment Groups

Age (year) and Sex	Azithromycin* (n = 48)	Conventional* (n = 48)
<5	10 (20.83)	12 (25)
5–8	23 (47.92)	21 (43.75)
9–12	12 (25)	10 (20.83)
>13	3 (6.25)	5 (10.42)
M/F	22/26	25/23

*Values in parentheses are percentages.

Discussion

Trachoma is a common disease that has disappeared in many parts of the world because of improved living conditions and hygiene. In trachoma-endemic areas, severe disease leading to scarring and blindness may be the result of frequent reinfection or persistent infection in those whose immune system does not mount an adequate response to clear the infection. Trachoma continues to be a serious public health threat in southeast Turkey.[12,13] *Chlamydia trachomatis* is an intracytoplasmic parasite and has a unique, long, life cycle. Chlamydia shows two

Table 2. Adverse Events Survey 7 Days After Azithromycin Treatment

Adverse Events	Number of Cases*
Abdominal pain	10 (20.83)
Diarrhea	5 (10.42)
Vomiting	3 (6.25)
Headache/body pain	2 (4.17)
Poor appetite	2 (4.17)
Fever	1 (2.08)

*Values in parentheses are percentages.

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Table 3. Clinical Success Rate (Resolution of Clinical Signs) in Azithromycin and Conventional Treatment Groups 3 and 6 Months After Start of Treatment

Time	Azithromycin* (n = 48)	Conventional* (n = 48)	Chi-Square
3 months	44 (91.67)	36 (75.00)	4.80†
6 months	43 (89.58)	33 (68.75)	6.32‡

*Values in parentheses are percentages.
†$P = .029$.
‡$P = .012$.

Table 4. Microbiological Success Rate (Direct Fluorescein Antibody Test Negativity) in Azithromycin and Conventional Treatment Groups 3 and 6 Months After Start of Treatment

Time	Azithromycin* (n = 48)	Conventional* (n = 48)	Chi-Square
3 months	42 (87.50)	34 (70.83)	4.04†
6 months	40 (83.33)	30 (62.50)	5.28‡

*Values in parentheses are percentages.
†$P = .045$.
‡$P = .022$.

distinctive forms during its life cycle: the elementary body and the reticulate body. The elementary body is an infectious particle that initiates its infectious cycle by attaching to the surface of a susceptible cell. Over a period of 6–8 hours, the particle enlarges, and undergoes reorganization to become a reticulate body. The reticulate body is noninfectious but metabolically active. Anti-chlamydial agents are only effective against reticulate bodies. These agents must penetrate into the cell, cytoplasmic inclusions, and finally into the reticulate body itself. Moreover, they must be maintained at high concentrations in tissues for a long period of time. Effective anti-chlamydial agents include tetracyclines, macrolides, and some of the fluoroquinolones.[14]

Recent advances in diagnostic and screening technology and azithromycin therapy will likely have a significant impact on the efficacy of disease control programs and the opportunity for eventual disease eradication. Azithromycin, with a half-life of 5 to 7 days, has excellent pharmacokinetic characteristics, such as increased bioavailability, lower incidence of gastrointestinal tract side effects, and increased concentration in mucus, macrophages, and tissues.[15] These characteristics allow for short course or single dosing, which alleviates the problem of patient noncompliance with multi-day regimens. The difficulty of applying ointment to the eyes of young children, the discomfort associated with its use, and the frequency of symptomless infection are other reasons for the failure of control programs based on topical therapy.

In this study, the 3-day course oral dose of azithromycin cured 83.33% of subjects with active trachoma by 6 months and was more effective than the conventional treatment. Possible adverse effects of the treatment were not serious and compliance was good in azithromycin-treated subjects. These observations have important implications for the control of trachoma.

Chumbley et al[16] suggested that there were no statistically significant differences between the trachoma cure rates of tetracycline eye ointment-, oral doxycycline-, and oral sulfamethoxypyridazine-treated groups. Dawson et al[17] reported that 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. Tabbara et al[18] reported that single-dose azithromycin is as effective as a 6-week course of topical tetracycline ointment in the treatment of active trachoma. These findings, when implemented, may help establish high compliance in treating trachoma and could contribute to the control of trachoma.

Bailey et al[19] reported that there were no significant differences in treatment effect, baseline characteristics, and re-emergent disease between tetracycline eye ointment and single oral dose azithromycin.

Malaty et al[20] suggested that there may be an extraocular reservoir of *Chlamydia trachomatis* infection in trachoma-endemic communities, for example, in the gut or nasopharynx of infected children, which may contribute to ocular infection. Systemic therapy, such as oral azithromycin, would be more likely to eradicate such a reservoir than would topical tetracycline.

Our finding of a significant difference between azithromycin and conventional treatment indicates that the two treatments have unequal efficacy.

In our study, reinfection rates were different for azithromycin and conventional treatment. The high rates of reinfection probably reflect the treatment strategy we adopted, the treatment of only active cases. It has been shown that subclinically infected individuals are an important source of reinfection in a rural area. Mass treatment of the whole community, which would be feasible with single-dose azithromycin could reduce the rate of reinfection through elimination of the reservoir of infection.

Rates of reinfection would then depend largely on migration patterns into and out of the communities treated, and on the success of behavioral interventions, such as face washing, which might reduce the rate of transmission.[16,21,22]

The high efficacy rate, low incidence of side effects, and shorter treatment duration suggest that azithromycin at a dosage of 10 mg/kg per day for 3 days is a viable alternative for the treatment of ocular *Chlamydia trachomatis* infections. The shorter treatment duration is likely to improve patient compliance. We believe that azithromycin given at this dosage represents a potential alternative for the treatment of active trachoma.

References

1. West SK, Munoz B, Turner WM. The epidemiology of trachoma in central Tanzania. Int J Epidemiol 1991;20:1088–92.
2. Thylefors B. Present challenges in the global prevention of blindness. Aust N Z J Ophthalmol 1992;20:89–94.
3. West SK, Munoz B, Lynch M, Kayongoya A, Mmbaga BBO, Taylor HR. Risk factors for constant, severe trachoma among preschool children in Kongwa, Tanzania. Am J Epidemiol 1996;143:73–8.
4. Salamon SM. Tetracyclines in ophthalmology. Surv Ophthalmol 1985;29:265–75.
5. World Health Organization. Strategies for the prevention of blindness in national programmes: a primary health care approach. Geneva: World Health Organization, 1984.
6. Dolin PJ, Faal H, Johnson GJ. Reduction of trachoma in a sub-Saharan village in absence of a disease control programme. Lancet 1997;349:1511–2.
7. McDonald PJ, Pruul H. Phagocyte uptake and transport of azithromycin. Eur J Clin Microbiol Infect Dis 1991;10:828–33.
8. Nahata MC, Koranyi DI, Gadgil SD. Pharmacokinetics of azithromycin in pediatric patients after oral administration of multiple doses of suspension. Antimicrob Agents Chemother 1993;37:314–6.
9. Taylor KI, Taylor HR. Distribution of azithromycin for the treatment of trachoma. Br J Ophthalmol 1999;83:134–5.
10. Thylefors B, Dawson CR, Jones BR. A simplified system for the assessment of trachoma and its complications. Bull World Health Organ 1987;65:477–83.
11. West SK, Rapoza P, Munoz B, Katala S, Taylor HR. Epidemiology of ocular chlamydial infection in a trachoma-hyperendemic area. J Infect Dis 1991;163:752–6.
12. Guraksin A, Gullulu G. Prevalence of trachoma in eastern Turkey. Int J Epidemiol 1997;26:436–42.
13. Negrel AD, Minassian DC, Sayek F. Blindness and low vision in southeast Turkey. Ophthalmic Epidemiol 1996;3:127–34.
14. Jones RB. New treatment for *Chlamydia trachomatis.* Am J Obstet Gynecol 1991;164:1789–93.
15. Ballow CH, Amsden GW. Azithromycin. The first azalide antibiotic. Ann Pharmacother 1992;26:1253–61.
16. Chumbley LC, Viswalingam ND, Thomson IM, Zeidan MA. Treatment of trachoma in the West Bank. Eye 1988;2:471–5.
17. Dawson CR, Schachter J, Sallam S, Sheta A, Rubinstein RA, Washton H. A comparison of oral azithromycin with topical oxytetracycline/polymyxin for the treatment of trachoma in children. Clin Infect Dis 1997;24:363–8.
18. Tabbara KF, Abu-el-Asrar A, al-Omar O, Choudhury AH, al-Faisal Z. Single dose azithromycin in the treatment of trachoma. A randomized, controlled study. Ophthalmology 1996;103:842–6.
19. Bailey RL, Arullendran P, Whittle HC, Mabey DCW. Randomized controlled trial of single-dose azithromycin in treatment of trachoma. Lancet 1993;342:453–6.
20. Malaty R, Zaki S, Said ME, Vastine DW, Dawson CR, Schachter J. Extraocular infections in children in endemic trachoma. J Infect Dis 1981;143:853–7.
21. Ward M, Bailey R, Lesley A, Kajbaf M, Robertson J, Mabey D. Persisting inapparent chlamydial infection in a trachoma endemic community in The Gambia. Scand J Infect Dis 1990;69(Suppl):137–48.
22. Taylor HR, West SK, Mmbaga BBO. Hygiene factors and increased risk of trachoma in central Tanzania. Arch Ophthalmol 1989;107:1821–5.