Outcome of azithromycin treatment of active trachoma in Omani schoolchildren

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حصيلة معالجة التراخوما النشيطة بالآزيثروميسين لدى الأطفال العُمانيين

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الخلاصة: أُجريت دراسةٌ أترابيَّةٌ استباقية شملت 386 من تلامذة الصف الأول من المدارس الابتدائية في عُمان من المُصابين بالتراخوما النشيطة مع 386 من الشواهد الذين يماثلونهم في كل شيء إلا في الإصابة بالتراخوما. وقد تلقّى جميع الأطفال التثقيف اللازم حول الوقاية من التراخوما، ثم عولجت حالات التراخوما بجرعة وحيدة من الآزيثروميسين عن طريق الفم (20 مغ/كغ)، ثم أعيد تقييم وضع التراخوما بعد 6 أسابيع ثم بعد 6 أشهر ثم بعد 12 شهراً. وقد زالت الجريبات والعلامات الالتهابية للحثر النشيط بعد مضي 6 أسابيع أو أكثر على المعالجة بالآزيثروميسين. وقد حدثت أفضل مستويات الوقاية من دورات عدوى التراخومالية التالية بعد 6 أشهر (85.2٪ من الحالات و99.0٪ من الشواهد خالية من العدوى) ثم تناقصت بعد 12 شهراً (66.7٪ من الحالات و98.2٪ من الشواهد خالية من العدوى). وقد تبيَّن أن التقييم السريري يمثِّل وسيلة مفيدة لتقييم استجابة حالات التراخوما النشيطة للمعالجة بالآزيثروميسين في أطفال المدارس في البلدان ذات الموارد المحدودة.

ABSTRACT A prospective cohort study was made of 386 first-grade primary-school children in Oman with active trachoma and 386 matched controls without trachoma. All children were educated about trachoma prevention. In addition, trachoma cases were treated with a single dose of oral azithromycin (20 mg/kg). Trachoma status was evaluated after 6 weeks, 6 months and 12 months. The follicles and inflammatory signs of active trachoma resolved 6 weeks or more after azithromycin treatment. The protection against subsequent trachoma infection cycles was optimal at 6 months (85.2% of cases, 99.0% of controls infection-free) but declined at 12 months (66.7% of cases, 98.2% of controls infection-free). Clinical evaluation seems to be a useful tool to evaluate the response of azithromycin to active trachoma cases in schoolchildren in a country with limited resources.

Issue du traitement du trachome évolutif par l'azithromycine chez des écoliers omanais

RESUME Une étude de cohorte prospective a été réalisée à Oman chez 386 écoliers en première année de primaire présentant un trachome évolutif et 386 témoins appariés sans trachome. Tous les enfants avaient été sensibilisés à la prévention du trachome. En outre, les cas de trachome ont été traités avec une dose unique d'azithromycine orale (20 mg/kg). Une évaluation du trachome a été effectuée après six semaines, six mois et douze mois. Les follicules et les signes inflammatoires du trachome évolutif se sont résorbés six semaines ou plus après le traitement par l'azithromycine. La protection contre les cycles suivants d'infection trachomateuse était optimale à 6 mois (85,2 % de cas, 99,0 % des témoins sans infection) mais diminuait à 12 mois (66,7% des cas, 98,2 % des témoins sans infection). L'évaluation clinique semble être un instrument utile pour évaluer la réponse à l'azithromycine des cas de trachome évolutif chez les écoliers dans un pays dont les ressources sont limitées.

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Introduction

Trachoma is still a leading infectious cause of blindness and ocular morbidity in the world [*1*]. In the policy document *Vision 2020—the right for sight* the World Health Organization has recommended that trachoma should be prioritized in national programmes [*2*]. The goal of elimination of blinding trachoma by 2020 could be achieved by adopting the SAFE trachoma control strategy (S: surgery for trichiasis, A: antibiotic treatment of active trachoma, F: facial cleanliness and E: environmental improvement) [*3*]. The global estimates in 2002 by the WHO suggest that nearly 84 million active trachoma cases need antibiotic treatment, 7.6 million trichiasis cases should be managed surgically and around 3 million cases of blindness are due to complications of trachoma. The Eastern Mediterranean Region has 11% of the active trachoma global pool and 22% of the trichiasis global pool [*4*]. A community-based study in Oman in 1996–97 showed that the population prevalence of active trachoma across all ages was 2.2% and that 1% of the population was suffering from trachomatous trichiasis [*5*].

Ocular infection with *Chlamydia trachomatis* can be effectively treated with oral azithromycin, which reaches therapeutic concentrations in ocular tissue at a dose of 20 mg/kg body weight [*6*]. Oral azithromycin also seems to have prophylactic properties. The 90% minimal inhibitory concentration for *C. trachomitis* can be detected in conjunctival tissues 14 days after administration of azithromycin. Hence, during this period, a child remaining at risk is likely to be protected from a second infection cycle [*7*]. The Nepal study showed that both targeted and mass treatment strategies using azithromycin significantly reduced the levels of trachoma in children 6 months after treatment [*8*].

The World Health Organization through the Global Alliance for Trachoma Control Initiative has provided this drug to many developing countries [*9*]. Both clinical and laboratory studies have shown that oral azithromycin treatment produces a high a clinical response, has minimal side-effects and achieves good compliance [*10–15*]. In 1999 the national eye health care programme at the Ministry of Health in the Sultanate of Oman introduced azithromycin for the treatment of active trachoma cases among first-grade primary children in all Omani schools. However, prior to the introduction of azithromycin treatment, no information was available on the clinical response to this regimen among the Omani population.

The present study was undertaken to evaluate the effect of single-dose azithromycin treatment on Omani schoolchildren with trachoma after 6 weeks, 6 months and 12 months compared with a randomly selected and matched control group of healthy children without treatment. It was hoped that the findings of the study would enable a review of the trachoma control initiatives in Oman.

Methods

Sample

The study was a prospective cohort analytical clinical study. All first-grade primary pupils in all the government schools in Oman (out of an annual school population of nearly 42 000 pupils) were screened during 2000–01. All children with active trachoma were entered in the study; 5% were lost to follow-up, leaving 386 cases. To control for trends in the disease over time, a pupil of the same age, sex and school class but without active trachoma was matched to each case using random

numbers and enrolled in a control group who received no treatment.

Investigators

The field staff and the supervisors of the eye health care programme were qualified medical graduates related to the school health programme; all were trained in standard eye examination. The average experience of the school health doctors was 42 months. The supervisors had more than 10 years of experience. Supervision of each phase of the study at regional and central level was carried out by the investigators.

Data collection

The field investigators visited all schools of their allotted area. They explained the purpose of screening and the revised regimen for active trachoma to the school authorities. Verbal consent of the school principal was obtained to undertake the screening and treatment. All first-grade primary pupils were listed and eye examination was performed in the classroom.

Standard tools for clinical examination and reporting were used. A focusing torch and 2.5 × ophthalmic loupe were used to examine the eye for trachoma. A swab stick was used to evert the eyelid. Spirit swabs were used to clean the fingertips of the examiner to avoid cross-infection.

The trachoma grades used in this study were those recommended by the World Health Organization [*16*] and specified in the 10th revision of the *International classification of diseases* [*17*]. More than 5 follicles of > 0.5 mm in size on the tarsal conjunctiva in either eye was classified as trachomatous inflammation, follicular (TF). Pronounced inflammatory thickening of the tarsal conjunctiva that obscured more than half of the normal deep tarsal vessels was considered as trachomatous inflammation, intense (TI). If one eye had TI and the other eye had TF, the child was classified as having TI. Presence of scarring in the tarsal conjunctiva was defined as trachomatous conjunctival scarring (TS). Absence of TF and TI grades or presence of TS at the time of follow-up was considered as successful outcome of the treatment. Presence of TF or TI on follow-up after 6 weeks and 6 months was considered as non-response to the treatment. Presence of TF and TI after 1 year was considered as either non-response to the treatment or re-infection.

A standard pre-tested form was used to record personal details and trachoma status. Children with active trachoma were weighed using a standard calibrated weighing machine. The quantity of azithromycin was calculated using 20 mg/kg body weight. To ensure that child was not allergic to routine medicines, the school health records were consulted. After the child's breakfast, an azithromycin suspension was prepared and given orally in the required dose. Any side-effects within 24 to 48 hours were recorded and these children were referred to the primary health centre.

During the follow-up visits at 6 weeks, 6 months and 12 months, a detailed eye examination to note trachoma status was performed by eye health care supervisors who were blind to the treatment status of the children. Information on each follow-up visit was collected on a standard form. New cases of active trachoma found during follow-up in cases or controls were treated with oral azithromycin.

Both cases and controls were exposed to health education about facial cleanliness and environmental improvement.

Data analysis

The data was computed using *Epi-Info*, version 6. The data was cleaned and checked for consistency. Analysis of the

study data was carried out using *SPSS*, version 9. The frequencies and their percentage proportions along with the 95% confidence intervals (CI), odds ratio (OR) and relative OR were calculated for validation.

Ethical considerations

As per the Helsinki Declaration for *International guidelines for biomedical research involving human subjects* issued in 1992, the following issues were addressed in this study. The consent of administrators in the Ministry of Health and schools were obtained. The children with eye problems detected during the study were provided with free treatment. The results of this study were used for the improvement of eye care of the study subjects and the national programme. The confidentiality of the study results was maintained.

Results

A total of 386 active trachoma cases detected in school screening in Oman and 386 randomly selected pupils without active trachoma at the time of screening were entered in the study.

The distribution of the cases by sex and region is given in Table 1: 207 (53.6%) were girls, 179 (46.4%) boys. The percentage of the cases in each region were: 47.7% in Dhakhiliyah, 27.7% in North Sharqiyah, 5.4% in South Sharqiyah, 10.1% in North Batinah and 9.1% in South Batinah.

At the start of the study, 375 (97.2%) of the cases were classified as TF and 9 (2.3%) as TI. Two children had less than 5 follicles of more than 0.5 mm size in the tarsal conjunctiva (TF_5).

Table 2 shows the trachoma status of cases at 6 weeks, 6 months and 12 months after azithromycin treatment compared with controls. Peak response to the azithromycin regimen was observed at 6 months (85.2% of cases with no active trachoma) and had declined by 12 months (66.6% of cases with no trachoma).

The trachoma status by sex is given in Table 3. Response to azithromycin treatment was significantly higher among girls than boys, especially at 6-months follow-

Table 1 **Distribution of the trachoma cases in 6-year-old schoolchildren by sex and region of Oman**

Region	Males		Females	
	No.	%	No.	%
Dhakhiliyah	77	43.0	107	51.7
North Sharqiyah	51	28.5	56	27.1
South Sharqiyah	10	5.6	11	5.3
North Batinah	18	10.1	21	10.1
South Batinah	23	12.8	12	5.8
Total	179	100.0	207	100.0

Table 2 **Active trachoma status of cases and control children at different follow-up times after azithromycin treatment**

Follow-up interval	Active trachoma No.	No active trachoma No.	%	95% CI
Cases (*n* = 386)				
6 weeks	151	235	60.9	54.7–67.1
6 months	57	329	85.2	81.4–89.0
12 months	129	257	66.6	60.9–72.5
Controls (*n* = 386)				
6 weeks	4	382	99.0	98.0–100.0
6 months	2	384	99.5	98.8–100.0
12 months	4	382	99.0	98.0–100.0

n = *total number of children.*

up (91.8% of girls with no active trachoma compared with 77.0% of boys).

Discussion

More than 95% of the active trachoma cases among first-grade Omani primary schoolchildren were enrolled in this study. In Oman, primary schooling is free and compulsory. Therefore, the study population is likely to be representative of the population of 6-year-old Omani children with and without active trachoma. The cases and the controls were from the same school class, age and sex and thus all factors except the presence of active trachoma and its standard treatment are likely to be similar in both groups. The investigators were experienced in trachoma grading and eye examination, which minimized the chances of misclassification, and use of the WHO trachoma grading reduced the risk of misclassification bias. Regional comparisons were not made because the samples in some regions were small and the overall prevalence of active trachoma was only around 1%.

There were some limitations to the study. Success and failure of treatment was assessed by clinical evaluation and not by laboratory tests and thus the outcomes might differ from studies that measure cure rate by laboratory tests. Due to the large number of staff involved in the screening, individual variation in the interpretation of trachoma cannot be ruled out, despite efforts for standardization. Children in the control group found to have active trachoma during follow-up were given treatment and this might have caused a slight underestimation of active trachoma rates in the control group during subsequent examinations.

The active trachoma status at follow-up was used to determine the clinical cure rate of azithromycin. Other factors such as improved health education in schools, focusing on face washing practices and sanitation habits, could also have contributed to the reduction of active trachoma

Table 3 **Active trachoma status of cases and control children by sex at different follow-up times**

Follow-up interval	No active trachoma				OR	95% CI	Relative OR
	Male (*n* = 179)		Female (*n* = 207)				
	No.	%	No.	%			
Cases							
6 weeks	98	54.7	137	66.2	1.62	1.05–2.49	1.0
6 months[a]	138	77.0	190	91.8	3.22	1.69–6.19	2.0
12 months[b]	94	52.6	155	75.0	2.70	1.72–4.24	1.7
Controls							
6 weeks, 6 months and 12 months	177	98.9	205	99.0	1.16	0.12–11.61	NA

n = *total number of children.*
[a]*Follow-up information on sex was missing for 1 child.*
[b]*Follow-up information on sex was missing for 8 children.*
NA = not applicable.

rates. However, in a short span of 1 year these other factors are unlikely to have made a substantial impact. Therefore, the reduced active trachoma rate on follow-up is most likely the result of the therapeutic/ prophylactic effect of azithromycin treatment. The presence of less than 1% active trachoma cases among controls at follow-up suggests that trachoma infection cycles are repeated in the community.

The large numbers of TF cases (97.2%) and only 2.3% of cases with TI grade suggest that the communicable stages of trachoma among 6-year-old Omani children are of mild intensity. The presence of some cases with less than 5 follicles in a trachoma endemic area favours inclusion of the TF$_{\circ}$ stage in the trachoma grading system. It could help the primary care staff in monitoring azithromycin distribution and evaluating the treatment outcome.

In the present study, around 40% of children still had signs of active trachoma (mainly follicles) after 6 weeks of treatment. A study in Gambia showed a clinical cure rate of 78% after 6 weeks [*10*] and 85% after 6 months. In other studies, where confirmation was based on clinical as well as laboratory tests, azithromycin was confirmed to have high rates of clinical cure as well infection reduction. The cure rate was reported to be 100% by 6 months in Saudi Arabia [*11,18*]. The infection rate was 5% after 2 months and 9% after 1 year through the immunofluorescence staining method. In Gambia, the cure rate was 65.4% measured using Giemsa staining and direct immunofluorescence staining [*10*]. The reduction in clinical activity was observed in 82% of the sample. Cases were tested by the lignase chain reaction method in Egypt [*12*], Gambia [*10*] and Tanzania [*13*]. Thus, the observation of rising clinical cure rate in the present study matches that of other studies. However, the low rate of clinical cure after 6 weeks does not match with high cure rates reported in other studies. This could be due to late resolution of trachoma follicles among the Omani children. A positive association of human leukocyte antigens (HLA) with susceptibility to blinding trachoma has been found in Omanis [*19*]. Genetic difference and the presence of different serologically typed *Chlamydia* spp. organisms could be the reason for the difference in trachoma severity and drug response in Oman.

The study of Egyptian children [*13*] had shown a clinical cure rate of 35% after 2 months of azithromycin treatment. However, using laboratory tests (immunofluorescence), the infection rate was found to decline from a pre-treatment rate of 33% to 5% at 2 months and 9% at the end of 12 months. Although in the present study the follow-up based on clinical examination after 6 weeks of treatment showed a high number of active trachoma cases, these may have the potential to infect others and may resolve clinically with time. A separate study to determine the cure rate of azithromycin treatment in Oman using laboratory testing for *C. trachomatis* should be undertaken.

As the tissue concentration of the drug gradually declines, the prophylactic role of azithromycin treatment declines with time [*15*]. Thus, at 12 months after treatment, in the absence of immunity against trachoma organisms, a person is at-risk for re-infection. The presence of TF and TI after 12 months observed in this study may be due to non-response to azithromycin or could be evidence of subsequent infection cycles.

Due to its affordability, repeatability and easy implementation, clinical evaluation seems to be the most practical method of evaluating the response to trachoma treatment at the primary care level. Clinical evaluation as used in this study could be a

monitoring tool to evaluate the impact of the 'A' antibiotic component of the 'SAFE' strategy for trachoma control in developing countries. However, the study findings suggest that clinical response to azithromycin should be evaluated after 6 months rather than after 6 weeks. Thus, annual school screening to identify and treat children with active trachoma should include follow-up of these positive cases after 6 months to evaluate their trachoma status and give a second dose of oral azithromycin if required.

The clinical cure rates in girls were significantly higher than in boys on follow-up at 6 weeks, 6 months and 12 months, especially at 6 months. In Oman, although active trachoma rates in both male and female children were reported to be equal, the blinding trachoma rate was significantly higher in females than males (unpublished report to WHO). Sex-related factors might influence the inflammatory response to trachoma infection in the Omani population.

The active trachoma rate of around 1% in first-grade Omani children suggests that, despite the high trachoma rates in the past, the infection pool in children might be declining and the country may be in an epidemiological transition phase. Although the active trachoma cases in Oman clinically fit the standard trachoma grading, the role of *C. trachomatis* in inflammatory conjunctival response might be different to other trachoma-endemic countries. A detailed pathological and microbiological study would enable scientists to understand the pathogenesis of trachoma in Oman and other countries with a similar trend of rapid decline of trachoma.

Conclusions

This study found a high clinical cure rate of a single-dose oral azithromycin for active trachoma among first-grade Omani schoolchildren both at short- and long-term follow-up. The active trachoma cases detected among control children during follow-up at 6 months and 1 year suggests active disease among contacts. Trachoma follicles resolve late after oral azithromycin treatment in Omani children. Clinical evaluation after 6 months seems to be a reliable tool for monitoring the impact of the 'A' (antibiotic) component of 'SAFE' trachoma control initiatives.

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