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Three-Year Outcomes of the Surgery for Trichiasis, Antibiotics to Prevent Recurrence Trial

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Objective: To determine whether treatment with oral azithromycin compared with topical tetracycline reduces the recurrence of trichiasis for up to 3 years following surgery for trichiasis.

Methods: The Surgery for Trichiasis, Antibiotics to Prevent Recurrence (STAR) trial is a randomized, single-masked, clinical trial conducted in southern Ethiopia, a region where trachoma is hyperendemic. A total of 1452 patients who underwent trichiasis surgery were randomly assigned at a 2:1 ratio to either a single dose of oral azithromycin (1 g) or topical tetracycline (twice per day for 6 weeks) following surgery.

Main Outcome Measures: Recurrence of trichiasis within 3 years following surgery.

Results: The rate of recurrence was 10% in the azithromycin group and 13% in the tetracycline group. The azithromycin group had a 22% reduction in recurrence of trichiasis 3 years after surgery compared with the tet-

racycline group ($P = .13$). Severity of entropion at baseline was the most significant predictor of recurrence of trichiasis at 3 years.

Conclusion: Trichiasis recurrence rates in the STAR trial remained low for up to 3 years following surgery. The protective effect of a single dose of azithromycin was less than at 1 year and, although not statistically significant, was still suggestive up to 3 years following trichiasis surgery.

Application to Clinical Practice: A single dose of azithromycin after surgery remains an integral component of the World Health Organization's strategy for the elimination of trachoma by the year 2020.

Trial Registration: clinicaltrials.gov Identifier: NCT00347776.

Arch Ophthalmol. 2012;130(4):427-431.

Published online December 12, 2011.

doi:10.1001/archophthalmol.2011.374

TRACHOMA IS THE LEADING INFECTIOUS cause of blindness, accounting for 15.5% of blindness worldwide.¹ It is caused by infection with the bacterium *Chlamydia trachomatis*, with years of repeated infection leading to a chronic follicular conjunctivitis, which may result in scarring of the eyelid and in-turned lashes rubbing the globe. This condition, known as trachomatous trichiasis, may result in corneal scarring and eventual blindness.¹ The World Health Organization (WHO) estimates that more than 6 million people are blind from trachoma. In regions where trachoma is hyperendemic, such as in Ethiopia, the prevalence of trichiasis in adults has been reported to be as high as 7%.² The WHO has endorsed a multifaceted strategy for eliminating trachoma by the year 2020; this strategy consists of surgical correction of trichiasis, antibiotic use, facial cleanliness, and environmental improvement (SAFE).^{3,4} Bilamellar

tarsal rotation is the current standard operation recommended by the WHO for correction of trichiasis because it has been shown to be more effective than electrolysis or cryoablation.⁵ However, trichiasis recurrence rates following surgery have been reported to be as high as 28% to 56% at 1 to 3 years in various studies.⁶⁻⁹

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One-year data from a randomized trial of patients with trichiasis (the Surgery for Trichiasis, Antibiotics to Prevent Recurrence [STAR] trial) demonstrated that a single 1-g dose of oral azithromycin compared with the administration of topical tetracycline twice per day for 6 weeks (control group) was effective in reducing the recurrence of trichiasis by 33% 1 year after surgery.¹⁰ The specific objectives of our study were to determine the 3-year rates of trichiasis recurrence in this

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Table 1. Characteristics of 1452 STAR Trial Participants at Baseline by Randomization Group

Characteristics	Randomization Group, No. (%)		P Value
	Tetracycline (n=484)	Azithromycin (n=968)	
Age, mean (SD), y	48.0 (12.8)	49.3 (13.1)	.08
Female	390 (80.6)	731 (75.5)	.03
Severity of entropion			
Mild	257 (53.1)	553 (57.1)	.31
Moderate	150 (31.0)	267 (27.6)	
Severe	77 (16.0)	148 (15.3)	
No. of lashes touching the globe ^a			
None	112 (23.1)	197 (20.4)	.55
1-3	103 (21.4)	237 (24.5)	
4-6	97 (20.2)	182 (18.8)	
7-9	45 (9.4)	97 (10.0)	
≥10	125 (26.0)	255 (26.3)	
IECW (surgeon) code			
1	248 (51.2)	461 (47.6)	.52
2	164 (33.9)	345 (35.6)	
3	66 (13.6)	153 (15.8)	
4	6 (1.2)	8 (0.8)	
5	0 (0.0)	1 (0.1)	

Abbreviations: IECW, integrated eye care worker; STAR, Surgery for Trichiasis, Antibiotics to Prevent Recurrence.

^aData are missing for 4 individuals in the tetracycline group.

trial and to assess whether the protective effect of azithromycin was still evident 3 years after surgery.

METHODS

The methods have been described in detail elsewhere.^{10,11} In summary, all patients with trichiasis who underwent surgery in the Wolayta Soddo Zone of southern Ethiopia between November 8 and December 30, 2002; between March 1 and May 10, 2003; and between October 8 and December 30, 2003, were screened for eligibility. Eligibility criteria¹ included the following: an age of 18 years or older,² the presence of trichiasis in at least 1 eye,³ and no previous report of surgery for trichiasis in the study eye. The exclusion criteria¹ were self-reported pregnancy,² documented allergy to tetracycline,³ and plans to move out of the region within 1 year. If both eyes were eligible, the study eye was assigned according to the randomly assigned study identification number: right eye if even and left eye if odd.

Bilamellar tarsal rotation was performed by local integrated eye care workers (ie, surgeons) specifically trained and certified for surgery using WHO guidelines.¹² Patients were randomly assigned at a 2:1 ratio to receive either a single dose of oral azithromycin (1 g) or 6 weeks of topical tetracycline ointment (twice daily). Within the azithromycin arm, patients were randomly assigned at a 1:1 ratio so that azithromycin would be given to (1) patients who underwent surgery for trichiasis¹ or (2) patients who underwent surgery for trichiasis and all their household members.² Because the 1-year data demonstrated that there was no difference in the outcomes between the 2 azithromycin arms, these subgroups have been combined into 1 group.¹⁰ The administration of the single dose of azithromycin was observed. Patients in the tetracycline group were provided with 2 tubes of tetracycline with instructions to apply the ointment to the surgical eye twice a day for 6 weeks following surgery.

Patients were randomly assigned to treatment groups, just prior to surgery. Envelopes containing randomly assigned,

masked treatment packages (tetracycline tubes or azithromycin pills) were labeled with sequential study identification numbers. Treatment assignments were blocked in variable sizes of 6 and 12, and safeguards were in place to ensure that each sequential patient received the next available study number. The treatment packages were not opened until after surgery. The office personnel responsible for randomization were not involved in the assessment of trichiasis severity at baseline, and the trained personnel who performed the outcome assessments were masked to treatment assignment.

The primary outcome, trichiasis recurrence in the study eye, was assessed at 2 weeks, 1.5 months, 6 months, 12 months, 18 months, 24 months, and 36 months following surgery. All assessments were performed clinically by a trained trachoma grader; each assessment was standardized to the senior project ophthalmologist. Trichiasis was defined as the presence of 1 or more lashes touching the globe and/or evidence of epilation, as specified by WHO criteria.¹³ Entropion was graded as mild (all lash bases visible), moderate (some lash bases visible but others not), or severe (all lash bases not visible).

All participants who did not have trichiasis 1 year after surgery received azithromycin or topical tetracycline again. There was no national trachoma control program or mass drug administration campaign in the Wolayta Soddo Zone of southern Ethiopia during the 3-year follow-up period.

Data analyses were performed using Stata version 9.0 (StataCorp). To incorporate the period in which recurrence occurred, life-table estimates of survival (free of trichiasis recurrence) were used. The primary comparison was cumulative incidence rate of recurrence in the tetracycline arm compared with that in the azithromycin arms. The log-rank test was used to assess differences in rates between the tetracycline and azithromycin groups. The Cox proportional hazards model was used to evaluate risk factors and adjust for confounders in predicting recurrences.

All participants provided written consent for our study, following a detailed oral and written description of all study procedures given in the local language. All procedures were approved by the Johns Hopkins Medical Institutions' institutional review board and by the Ethiopian Science and Technology Committee's National Ethical Clearance Committee. The trial is registered at clinicaltrials.gov (NCT00347776).

RESULTS

A total of 1452 participants were enrolled in the trial, with 484 in the tetracycline group and 968 in the azithromycin group. There was a slightly higher percentage of female patients in the tetracycline group than in the azithromycin group (80.6 vs 75.5%; $P=.03$) (**Table 1**). Otherwise, study participants were similar between the 2 groups with respect to age, severity of entropion, and severity of trichiasis. Three integrated eye care workers performed more than 99% of the surgical procedures, operating on a similar percentage of patients in both the control and treatment groups. Surgeons 4 and 5 only performed 15 surgical procedures in total and thus were not included in the multivariate analyses.

At the 3-year follow-up, the retention rate was more than 90% in each group (**Figure 1**), with 46 patients lost to follow-up in the tetracycline group and 84 patients lost to follow-up in the azithromycin group. The patients who were randomly assigned to receive oral azithromycin had a longer time to trichiasis recurrence at all time points compared with the patients who were randomly assigned to receive topical tetracycline, although this difference was not

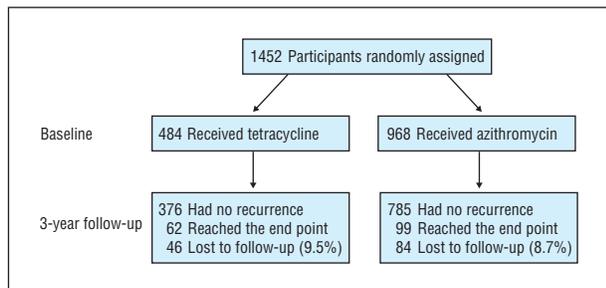


Figure 1. Flowchart of participants enrolled in the Surgery for Trichiasis, Antibiotics to Prevent Recurrence trial, at baseline and 3-year follow-up.

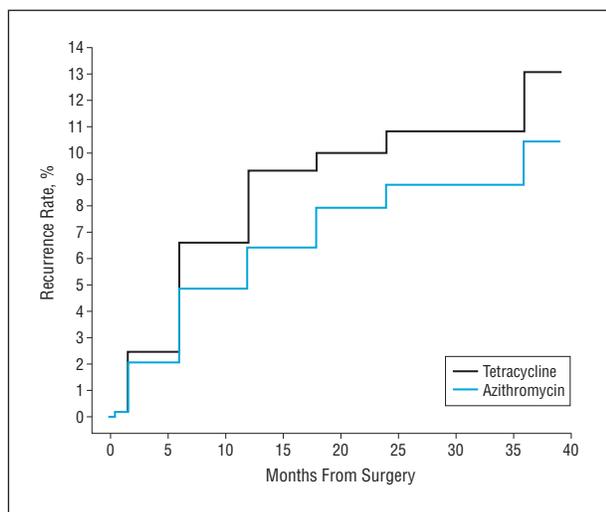


Figure 2. Cumulative incidence of recurrence of trichiasis by treatment group ($P=.11$, determined by use of the log-rank test).

statistically significant by 3 years (**Figure 2**). At 3 years, the incidence of recurrence was 10% in the azithromycin group vs 13% in the topical tetracycline group.

In a univariate analysis, predictors of trichiasis recurrence at 3 years included older age (hazard ratio, 1.01 [95% CI, 1.00-1.03]) and severity of entropion prior to surgery (hazard ratio, 1.74 [95% CI, 1.20-2.53] for moderate entropion and 2.98 [95% CI, 2.03-4.38] for severe entropion) (**Table 2**). Male sex was associated with increased recurrence (hazard ratio, 1.37 [95% CI, 0.96-1.93]), as was surgeon 3 (hazard ratio, 1.49 [95% CI, 0.97-2.27]).

The variables in the univariate analysis with $P < .10$ were included in the multivariate model. After adjusting for age, sex, surgeon, baseline severity of entropion, and the number of lashes touching the globe, treatment with azithromycin was protective against trichiasis recurrence compared with treatment with topical tetracycline, although this difference was not statistically significant (hazard ratio, 0.78 [95% CI, 0.56-1.07]) (**Table 3**). Only being a male patient and having severe entropion at baseline were associated with trichiasis at the 3-year follow-up.

COMMENT

Surgical correction of trichiasis is an integral part of the WHO effort to eliminate blindness from trachoma by the

Table 2. Univariate Analysis Predicting Cumulative Trichiasis Recurrence to 3 Years

Characteristic	Hazard Ratio (95% CI)
Age, y	1.01 (1.00-1.03)
Male	1.37 (0.96-1.93)
Severity of entropion	
Mild	1 [Reference]
Moderate	1.77 (1.20-2.53)
Severe	2.98 (2.03-4.38)
No. of lashes touching the globe	
None ^a	1 [Reference]
1-3	0.46 (0.27-0.78)
4-6	0.64 (0.38-1.05)
7-9	0.90 (0.51-1.59)
≥ 10	1.16 (0.77-1.73)
IECW (surgeon) code	
1	1 [Reference]
2	1.18 (0.84-1.68)
3	1.49 (0.97-2.27)
Treatment with azithromycin vs tetracycline	0.80 (0.58-1.10)

Abbreviation: IECW, integrated eye care worker.
^aIncludes those who may be epilating eyelashes.

Table 3. Multivariate Analysis Predicting Cumulative Trichiasis Recurrence to 3 Years

Characteristic	Hazard Ratio (95% CI)
Age, y	1.01 (1.00-1.02)
Male	1.52 (1.06-2.17)
Severity of entropion	
Mild	1 [Reference]
Moderate	1.57 (1.07-2.32)
Severe	2.55 (1.67-3.90)
No. of lashes touching the globe	
None ^a	1 [Reference]
1-3	0.61 (0.35-1.06)
4-6	0.85 (0.51-1.43)
7-9	1.02 (0.57-1.82)
≥ 10	1.09 (0.73-1.64)
IECW (surgeon) code	
1	1 [Reference]
2	1.15 (0.81-1.63)
3	1.55 (1.01-2.37)
Treatment with azithromycin vs tetracycline	0.78 (0.56-1.08)

Abbreviation: IECW, integrated eye care worker.
^aIncludes those who may be epilating eyelashes.

year 2020. However, recurrence rates following surgery for trichiasis have been reported to be disappointingly high. A 4-year prospective study¹⁴ in the Gambia found the rate of recurrence of trichiasis following posterior lamellar tarsal rotation to be 41% at 4 years, with the majority of recurrences occurring during the first 6 months after surgery. A study⁹ in Oman demonstrated that, at 3.1 years of follow-up, 61.8% of patients who underwent bilamellar tarsal rotation had a recurrence of trichiasis. Early recurrence, defined as 0 to 3 months following surgery, is thought to be due to surgical factors such as specific technique, whereas late recurrence is thought to be due to progressive scarring.¹⁵ The reported risk factors for recurrent trichiasis are tarsal conjunctival inflammation and

severe trichiasis or entropion at baseline.^{8,14} However, the overall 3-year recurrence rate in the STAR trial remained low when compared with other reported studies. Even the control group had a recurrence rate of only 13% at 3 years. We can only speculate on the reasons for the low recurrence rate. First, the surgeons in the STAR trial were specifically trained and had to be certified for this trial according to WHO guidelines.¹² This likely eliminated the large surgeon variability observed with other trials^{6,7,9,14} and decreased the surgeon-related recurrence at the outset. Second, suture removal was delayed until 2 weeks after surgery, as opposed to 1 week, on the recommendation of a member of the Data Safety and Monitoring Committee. This delay may have created a stronger tissue bond during wound healing. Finally, eyes that had previously underwent surgery for trichiasis were excluded from the STAR trial, and these eyes are the most difficult surgery cases with high risk of recurrence.

Previous analysis of the STAR data at 1 year showed that a single 1-g dose of oral azithromycin after surgery for trichiasis reduced trichiasis recurrence rates by 33% compared with the administration of topical tetracycline for 6 weeks.¹⁰ At 3 years, the protective effect of azithromycin was still evident, with a 22% reduction in recurrence rate from 13% to 10% when compared with topical tetracycline, although this difference was no longer statistically significant at 3 years. We are underpowered to detect a relative difference of 22% with such a low recurrence rate and with the limited loss to follow-up at this point. Even with more than 90% follow-up, our power to detect a difference of 22% was 55%.

The baseline characteristics of the patients included in the STAR trial have been published elsewhere.¹⁶ There was a high rate of severe disease at baseline, with 40% of patients having 5 or more lashes touching the globe and 44% of patients with moderate to severe entropion at baseline. Similar to the results at 1 year,¹⁰ moderate or severe entropion at baseline was found to be a significant risk factor for trichiasis recurrence at 3 years, thus emphasizing the need for early surgical correction. In our multivariate model, male sex was found to be a significant risk factor for trichiasis recurrence at 3 years, a pattern that was also demonstrated in the 1-year results. This may be related to differences in sex behavior because men were anecdotally observed to be more likely than women to have removed bandages at follow-up and thus may have been more likely to be exposed to infection, despite instructions to leave the bandage in place.¹⁷

There was no evidence of any difference in outcome by surgeon at the 1-year follow-up, and there was no statistically significant difference in recurrence by surgeon at the 3-year follow-up. However, there is a suggestion that 1 surgeon had a higher recurrence rate compared with the other surgeons at 3 years. It is unclear why such a difference would be more obvious at this point in time after the surgery and not at the 2-week, 6-week, 6-month, or 1-year assessment. The fact that the majority of cases of recurrence by any surgeon had occurred by 1 year suggests that a 1-year follow-up is adequate to determine outcomes for surgical audit. Patients should still be informed that recurrence is a possibility, and they should be urged to return to their doctor at the earliest onset of recurrence.

Patients who did not have a recurrence of trichiasis by 1 year were treated again with either azithromycin or topical tetracycline, after the examination. Not everyone received the same drug as originally assigned, with 33% of those originally receiving azithromycin receiving topical tetracycline at 1 year and with 17% of those originally assigned to topical tetracycline receiving oral azithromycin. Thus, some of the low incidences of recurrence overall may be the result of patients receiving treatment again at 1 year, but we cannot ascertain the effect because everyone was treated again.

Analysis of the STAR trial data at 1 year demonstrated that infection with *Chlamydia trachomatis* after treatment was not a risk factor for recurrence of trichiasis following surgery.¹⁰ Data are not available for the 3-year end point because ocular swab specimens were not collected at the time. One reason that lower rates of *C trachomatis* infection were not demonstrated in the azithromycin group compared with the tetracycline group may be that ocular swab specimens were only collected at 1.5 months and then at the point of trichiasis recurrence or at 12 months; thus, cases of infection in between these time points may not have been identified. In addition, the overall rates of infection were low, thus making it difficult to detect a difference between the groups. It is possible that treatment with azithromycin may play a role in preventing scar formation after surgery because anti-inflammatory effects have been described in the literature.^{10,18} However, studies⁸⁻¹⁰ have demonstrated that recurrence of trichiasis after surgery was highest in areas with the greatest prevalence of trachoma. It is not clear whether this is a result of persistent infection vs reinfection after surgery, and therefore this issue of recurrence requires further investigation.

In our study, the single dose of azithromycin administered was observed, and thus compliance was 100%. With the tetracycline group, only the first application of ointment was observed, and data on compliance for the next 6 weeks were not collected. It is possible that increased compliance in the azithromycin group may have contributed to the superior effect of azithromycin demonstrated in our trial. However, this advantage would also be applicable in a real-world setting because compliance with a single dose of oral azithromycin would be easier than compliance with a twice daily application of ointment for 6 weeks. In addition, although the cost of oral azithromycin is greater than the cost of topical tetracycline ointment (\$4.60 vs 30¢ per child), oral azithromycin is readily available in sub-Saharan Africa through mass donation programs.¹⁹

In conclusion, a single dose of oral azithromycin after surgery has been shown to be superior to topical tetracycline in protecting against the recurrence of trichiasis for up to 1 year, and some evidence is presented suggesting that the protective effect is evident for up to 3 years after surgery for trichiasis. Treatment with azithromycin thus remains an important component of the SAFE strategy for the eradication of trachoma.

Submitted for Publication: July 1, 2011; final revision received October 5, 2011; accepted October 12, 2011.

Published Online: December 12, 2011. doi:10.1001/archophthalmol.2011.374. This article was corrected on February 14, 2012.

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Author Contributions: Dr West had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This study was funded by grant EY13878 from the National Eye Institute.

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