Trimethoprim-Sulfamethoxazole Versus Placebo to Reduce the Risk of Recurrences of *Toxoplasma Gondii* Retinochoroiditis: Randomized Controlled Clinical Trial

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• PURPOSE: **To compare the effects of trimethoprim-sulfamethoxazole vs placebo in reducing the risk of recurrences of *Toxoplasma gondii* retinochoroiditis.**

• DESIGN: **Single-center, prospective randomized double-masked clinical trial.**

• METHODS: **A total of 95 patients from Campinas, Brazil, with active recurrent *Toxoplasma gondii* retinochoroiditis were included. The initially active toxoplasmosis lesions were successfully treated in all cases using trimethoprim-sulfamethoxazole (800 mg/160 mg) twice daily for 45 days. Subsequently, 5 patients dropped out of the study. The remaining patients were randomized to Group 1 (trimethoprim/sulfamethoxazole tablet every 2 days) or Group 2 (identical placebo tablet every 2 days). Randomization was 1:1, was stratified by sex, and used block sizes of 4. The primary outcome was recurrent toxoplasmosis retinochoroiditis within 1 year, and the secondary outcome was a 1-year change in best-corrected visual acuity (BCVA) (ETDRS chart).**

• RESULTS: **The incidence of recurrent toxoplasmosis retinochoroiditis within 12 months was 0 of 46 (0%) and 6 of 47 (12.80%) in the trimethoprim-sulfamethoxazole and placebo groups, respectively ($P = .026$). Visual acuity improvements in the 2 groups were similar. No treatment-limiting toxicity was observed.**

• CONCLUSIONS: **Trimethoprim/sulfamethoxazole therapy resulted in a 100% reduction in the recurrence of *Toxoplasma gondii* retinochoroiditis over 1 year of treatment. (Am J Ophthalmol 2014;157:762–766.**

TOXOPLASMOSIS IS MOST LIKELY THE MOST COMMON cause of posterior uveitis in immunocompetent individuals.[1,2] This disease can affect all age groups and both sexes, and ocular involvement can occur without any significant evidence of systemic disease.[3,4] During the chronic phase of toxoplasmic infections, short and usually self-limiting periods of parasite reactivation regularly occur and cause the typical presentation of acute recurrent toxoplasmic retinochoroiditis.[5]

Visual acuity and the number of chorioretinal lesions[6] are commonly used as measures of the long-term burden of ocular toxoplasmosis. Antibiotic treatment primarily aims to reduce the risk of permanent visual loss, recurrent retinochoroiditis, and the severity and duration of acute symptoms. There is uncertainty about the effectiveness of antibiotic treatment.[7]

There is no universally accepted treatment approach for ocular toxoplasmosis, and one of the current options is the sulfonamide group of drugs, which is effective against tachyzoite forms but which has little effect on bradyzoites, resulting in latent foci of the disease that are responsible for its recurrence.[8–10]

Despite the fact that newly developed drugs decrease the number of tissue cysts in experimental and animal studies, prevention of recurrent attacks of ocular toxoplasmosis has not yet been achieved.[11]

In an open-label trial, Silveira and associates[10] suggested that intermittent treatment with trimethoprim-sulfamethoxazole could reduce the rate of recurrent toxoplasmic retinochoroiditis. The patients were randomized to treatment with 1 tablet of trimethoprim-sulfamethoxazole every 3 days or to observation without treatment and were followed monthly for up to 20 consecutive months for clinical signs of disease recurrence. Recurrences developed in 4 treated patients (6.60%) and in 15 controls (23.80%). The weaknesses of their study were the facts that control subjects did not receive placebo and that subjects were not examined in a masked fashion; these factors may affect the ability to interpret drug side effects, and may also affect follow-up and introduce bias during the examinations.

The purpose of this double-masked trial was to compare the effects of trimethoprim-sulfamethoxazole vs placebo in reducing the risk of recurrences of *Toxoplasma gondii* retinochoroiditis.

METHODS

THIS STUDY WAS A SINGLE-CENTER, PROSPECTIVE RANDomized double-masked clinical trial. Ethics committee

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(Institutional Review Board) approval was obtained, and all participants gave informed consent (National Bioethics Commission of Brazil identifier: 0613.0.146.000-10). The trial was registered in October 2011 and began in November 2011 (Influence of Trimethoprim-Sulfamethoxazole for the Recurrence of Ocular Toxoplasmosis; clinicaltrials.gov identifier: NCT01449877; http://clinicaltrials.gov/show/NCT01449877).

A total of 100 patients were recruited from a public hospital in the city of Campinas, in Brazil. All patients were followed up for 12 months. Inclusion criteria were active recurrent *Toxoplasma gondii* retinochoroiditis (a new focus of necrotizing retinochoroiditis with active inflammation either adjacent to or remote from preexisting retinochoroidal scars, with positive IgG for toxoplasmosis). Patients who were under 18 years of age, immunocompromised (eg, acquired immunodeficiency syndrome), or undergoing immunosuppressive treatments, or who had concomitant retinochoroiditis from other causes (eg, tuberculosis), were excluded.

All patients were treated for active toxoplasmic retinochoroiditis with 1 tablet of trimethoprim-sulfamethoxazole (800 mg/160 mg) 2 times daily for 45 days, and all lesions were healed after this treatment. Subsequently, 5 patients dropped out of the study. The remaining patients were randomly assigned to Group 1 (1 trimethoprim-sulfamethoxazole tablet every 2 days) or Group 2 (1 identical placebo tablet containing starch without any active ingredients every 2 days). Randomization was 1:1 and was stratified by sex, and block sizes of 4 were used. One nurse generated the random allocation sequence, and another nurse enrolled and assigned the participants in the interventions in a masked fashion.

The trial was sponsored by Fundação de Amparo a Pesquisa do Estado de São Paulo, protocol 2010/15980-2. Trimethoprim/sulfamethoxazole tablets cost US$0.31 each and placebo tablets cost US$0.15.

Data were collected by means of a medical history form completed by the physician at the time of the first medical examination. Best-corrected visual acuity (BCVA) with Early Treatment Diabetic Retinopathy Study (ETDRS) charts, biomicroscopy, tonometry, indirect ophthalmoscopy, recurrence of *Toxoplasma gondii* retinochoroiditis, and medical events were recorded monthly on a standardized form by a member of the medical staff in a masked fashion.

The primary outcome was recurrent toxoplasmosis retinochoroiditis within 12 months (Figure 1), and the secondary outcome was a change in BCVA (ETDRS chart) over 12 months.

Sample size calculations based on presumed recurrence rates of 0% and 15% in the treatment and placebo groups, respectively, indicated that a sample size of 35 in each group would be significant for detecting a difference of this magnitude with a power of 80% and type 1 error probability of 5%. However, to account for losses in follow-ups and based on feedback obtained after the initiation of the study, 95 patients were enrolled.[10]

Descriptive statistics were calculated. Continuous data were expressed as the mean values, standard deviation (SD), and ranges. Between-group differences of continuous variables were compared using the Mann-Whitney *U* test, and categorical variables were compared using χ^2 test or Fisher exact test when appropriate. Analyses were conducted using SPSS version 21 (IBM Corporation, Armonk, New York, USA) and SOFA version 1.3.5 (Statistics Open For All; AGPL3 Free Software, accessed at http://www.sofastatistics.com/downloads.php). *P* values are 2-tailed. Statistical significance was considered at the .05 level.

RESULTS

BETWEEN AUGUST 24, 2011, AND AUGUST 28, 2012, 95 patients were enrolled at a public hospital in Campinas, Brazil, and were randomized to trimethoprim/sulfamethoxazole (47 patients) or placebo (48 patients) therapy. A total of 93 patients completed the 12 months of follow-up (1 lost to follow-up in each group; Figure 1). The mean age was 33 (SD 13) years (median 33), and 53 patients were female. The age and sex distributions were similar between the groups (Table 1).

The incidence of recurrent toxoplasmosis retinochoroiditis within 12 months was 0 of 46 (0.00%) and 6 of 47 (12.80%) in the trimethoprim-sulfamethoxazole and placebo groups, respectively ($P = .03$).

The mean changes in BCVA were 21 (SD 18) letters (median: 15) in the trimethoprim-sulfamethoxazole group and 22 (SD 16) letters (median: 23) in the placebo group ($P = .90$) (Figure 2).

No treatment-limiting toxicity was observed.

The mean interval between the pre-enrollment recurrence episode and the first recurrence observed during study follow-up was 146 (SD 93) days (median: 140) (Figure 3). The demographic data from the patients with new recurrence of toxoplasmosis retinochoroiditis are shown in Table 2.

DISCUSSION

THE INCIDENCE OF RECURRENT TOXOPLASMOSIS RETINOchoroiditis was statistically significantly higher in patients treated with placebo compared with patients who received 1 trimethoprim-sulfamethoxazole tablet every 2 days. (The initially active toxoplasmosis lesions were successfully resolved in all cases using trimethoprim-sulfamethoxazole 2 times daily for 45 days.) These findings are consistent with the open-label trial conducted by Silveira and associates, which suggested that suppressive treatment with this

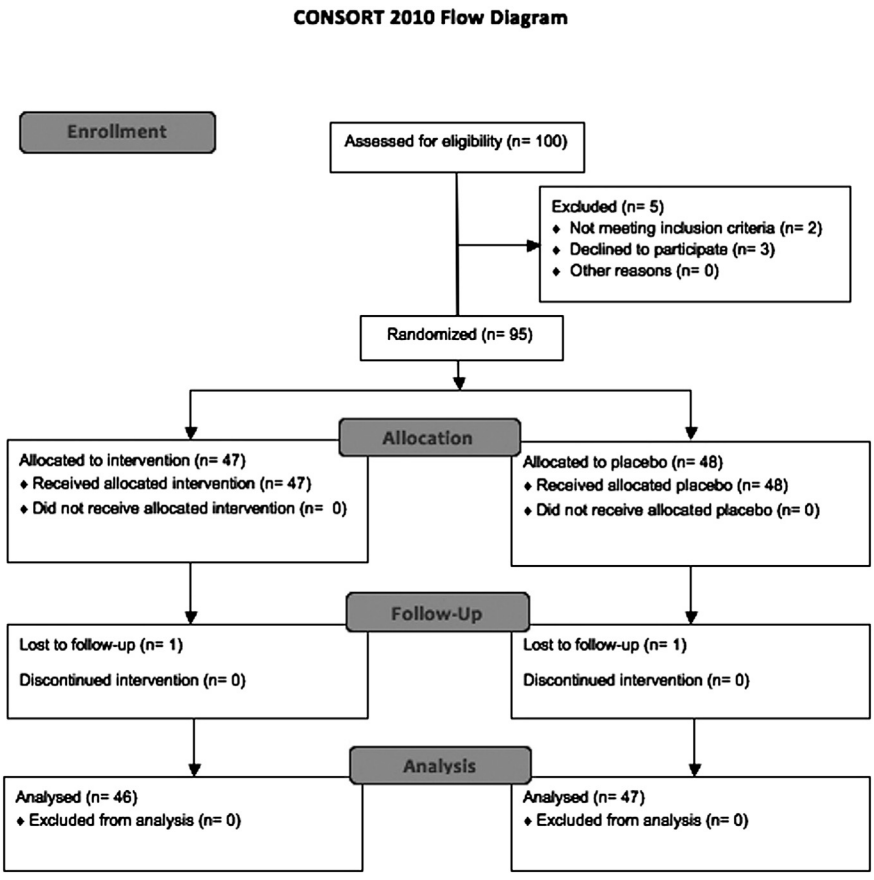

FIGURE 1. Trimethoprim-sulfamethoxazole vs placebo to reduce the risk of recurrences of *Toxoplasma gondii* retinochoroiditis: CONSORT flow diagram.

drug combination could reduce the rate of recurrent toxoplasmic retinochoroiditis.[10,12]

It was hypothesized that long-term suppressive treatment with trimethoprim-sulfamethoxazole suppresses proliferation of occasional parasites that emerge from tissue cysts, thus allowing for the establishment of effective host control before the parasite can proliferate to an extent that causes clinically apparent lesions.[10]

There were no significant differences in the change in BCVA between the 2 groups. Although recurrent toxoplasmosis retinochoroiditis is a prevalent worldwide disease and an important cause of blindness,[6] our results failed to demonstrate a benefit of the intermittent treatment for the final BCVA. It is possible that the difference in BCVA would occur if there were a larger sample or longer follow-up period. Repeated episodes of retinochoroiditis seem likely, eventually, to take a toll on vision.

Trimethoprim-sulfamethoxazole was chosen for this study based on its convenience, low cost, and low rate of side effects. The frequency of administration was chosen empirically but is similar to a previous study.[10]

One of the trial limitations is its limited duration of follow-up, which was attributable to logistical constraints. Although the study seems to add support for the ability to suppress recurrences during treatment, a study with long-term follow-up would be required to confirm any long-term benefits. Similarly, the study did not reveal a difference in visual outcomes over 1 year. Although it is unclear whether visual outcomes would have been better with treatment over a longer period of time, the observation that visual acuity was reduced among the eyes with recurrence vs those without recurrence suggests that trimethoprim-sulfamethoxazole treatment might benefit vision if longer-term therapy were used. The combination of trimethoprim-sulfamethoxazole is generally well tolerated, with less than 3% of patients experiencing side effects, although long-term use of trimethoprim-sulfamethoxazole may lead to the development of drug-resistant bacteria and adverse side effects, the most frequent of which are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria); however, fatalities, although rare, have occurred owing to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias.[13,14] One additional

TABLE 1. Trimethoprim-Sulfamethoxazole Versus Placebo to Reduce the Risk of Recurrences of *Toxoplasma Gondii* Retinochoroiditis: Demographic Data

	Trimethoprim-Sulfamethoxazole (n = 47)	Placebo (n = 48)	*P*
Age (y): mean (SD), median	34 (13), 33	33 (14), 33	.78[a]
Male/female ratio	20/27	22/26	.75[b]
Baseline BCVA	58 (SD 20) letters (20/80)	52 (SD 18) letters (20/100)	.17[a]
12-month BCVA	79 (SD 16) letters (20/25)	74 (SD 18) letters (20/32)	.17[a]

BCVA = best-corrected visual acuity; SD = standard deviation.
[a]Mann-Whitney *U* test.
[b]χ^2 test.

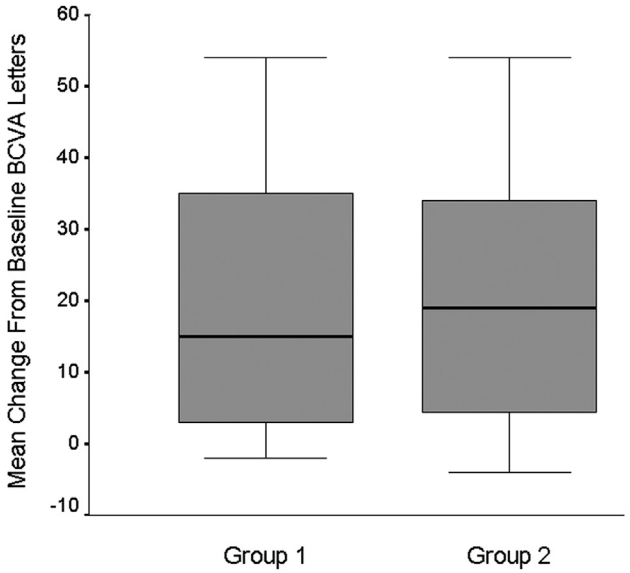

FIGURE 2. Trimethoprim-sulfamethoxazole vs placebo to reduce the risk of recurrences of *Toxoplasma gondii* retinochoroiditis: changes of best-corrected visual acuity (BCVA). Group 1 = trimethoprim-sulfamethoxazole; Group 2 = placebo.

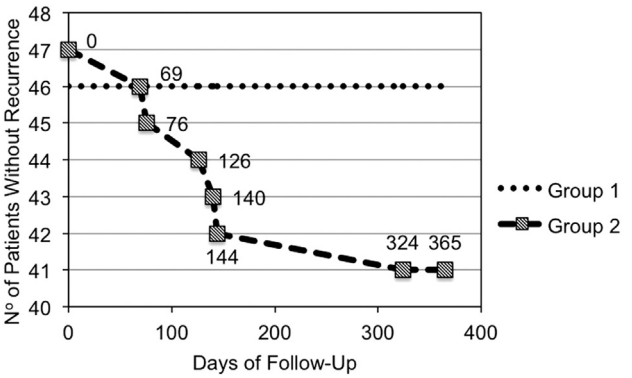

FIGURE 3. Trimethoprim-sulfamethoxazole vs placebo to reduce the risk of recurrences of *Toxoplasma gondii* retinochoroiditis: graph of time to recurrence by treatment assignment. Group 1 = trimethoprim-sulfamethoxazole; Group 2 = placebo.

TABLE 2. Characteristics of Patients Observed to Have Recurrent Toxoplasmosis Retinochoroiditis During Follow-up Versus Those Without Recurrence

	New Recurrence (n = 6)	No Recurrence (n = 87)	*P*
Age (y): mean (SD), median	30 (9), 33	34 (13), 33	.51[a]
Male/female ratio	1/5	40/47	.22[b]
Baseline BCVA	44 (SD 16) letters (20/125)	56 (SD 19) letters (20/80)	.33[a]
12-month BCVA	70 (SD 15) letters (20/40)	77 (SD 18) letters (20/32)	.50[a]

BCVA = best-corrected visual acuity; SD = standard deviation.
[a]Mann-Whitney *U* test.
[b]Fisher exact test.

concern is that generalizability of the trial findings is limited to people with severe disease or those with high risks of recurrence or vision-threatening lesions.

The most important application to clinical practice of our results is that adjuvant prophylactic therapy with trimethoprim-sulfamethoxazole may reduce the recurrences of *Toxoplasma gondii* retinochoroiditis. As suggested by other authors,[10,15] trimethoprim-sulfamethoxazole therapy may be appropriate for specific individuals who have demonstrated histories of frequent and/or severe recurrences. It should also be considered for people who are at greatest risk for vision loss, such as those with retinochoroidal scars adjacent to the fovea, where any reactivation can result in profound vision loss.

These results suggest a potential approach for preventing the recurrence of this frequent cause of intraocular inflammation. Further research and a longer follow-up period are recommended to allow for the evaluation of the possible beneficial effect of long-term treatments at the prevention of recurrences in immunocompetent adults, as well as in congenitally acquired infections and in immunodeficient patients.

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Biosketch

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