Trimethoprim-Sulfamethoxazole Versus Placebo in Reducing the Risk of Toxoplasmic Retinochoroiditis Recurrences: A Three-Year Follow-up

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• PURPOSE: **To compare the effects of 1 year of treatment with trimethoprim/sulfamethoxazole (TMP-SMZ) vs a placebo in reducing the risk of toxoplasmic retinochoroiditis recurrences during a 3-year follow-up period.**

• DESIGN: **Randomized, double-masked clinical trial.**

• METHODS: **This cohort included 141 volunteers recruited in Campinas, Brazil. Inclusion criterion was unilateral active recurrent toxoplasmic retinochoroiditis. All volunteers were treated with 1 tablet of TMP-SMZ (160 mg/800 mg) twice daily for 45 days, and all lesions healed after this treatment. After this initial treatment, the volunteers were randomly assigned to Group 1 (1 TMP-SMZ tablet every 2 days for 311 days) or Group 2 (1 identical placebo tablet containing starch with no active ingredients every 2 days for 311 days). At the second- and third-year follow-up appointments, none of the volunteers received treatment unless a new recurrence episode had occurred. The primary outcomes were recurrent toxoplasmic retinochoroiditis within the first year of follow-up and recurrent toxoplasmic retinochoroiditis within the third year of follow-up.**

• RESULTS: **The cumulative probability of recurrence at 1, 2, and 3 years of follow-up were, respectively, 13.0% (9/69), 17.4% (12/69), and 20.3% (14/69) in the placebo group and 0% (0/72) in the TMP-SMZ group ($P < .001$, log-rank test). There was no case of multiple recurrences in the same individual. No treatment-limiting toxicity or side effects were observed in either group. New recurrences were more frequent among female volunteers.**

• CONCLUSIONS: **TMP-SMZ may be used safely for prophylaxis of recurrent toxoplasmic retinochoroiditis, with long-term benefits. (Am J Ophthalmol 2016;170: 176–182. © 2016 Elsevier Inc. All rights reserved.)**

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OCULAR TOXOPLASMOSIS IS RESPONSIBLE FOR most cases of infectious posterior uveitis in the world and is an important cause of blindness and visual impairment.[1,2]

The exact causes and pathogenesis of recurrences in ocular toxoplasmosis are not known. During the chronic phase of toxoplasmic infections, short and usually self-limiting periods of parasite reactivation regularly occur and cause the typical presentation of recurrent toxoplasmic retinochoroiditis. The mechanisms of action involved in the switch from latent to proliferative forms of parasites are not well understood. Numerous hypothetical triggers have been suggested, including immune response and hormonal status of the host, human leukocyte antigen type, autoimmune or hypersensitivity reactions to exposed toxoplasmic antigens, and parasite-related factors, such as the mechanical rupture of cysts caused by parasite multiplication, the release of toxins or lytic enzymes by the parasite, or reinfections with other strains of parasites.[3–5]

It has been postulated that recurrences are associated with the proliferation of live organisms that emerge from tissue cysts. Over time, the viability of tissue cysts in the retina decreases and the cysts eventually die, reducing the pool of cysts from which reactivation can occur. As a consequence, the probability of recurrences decreases after each active episode. This factor supports the argument that an increased risk of recurrence appears during the first year following active retinochoroiditis. Other factors that have been argued as having an influence on recurrences include changes in tissue cysts with reduced release of parasites or antigens, trauma, endocrine fluctuations, and transient humoral or cellular immunoreactivity.[6,7]

Silveira and associates[8] and Commodaro and associates[9] assert that further research is required to evaluate the possible beneficial effect of long-term treatments on the prevention of ocular toxoplasmosis recurrences. It has been hypothesized that long-term treatment with trimethoprim-sulfamethoxazole (TMP-SMZ) suppresses the proliferation of the occasional parasites that emerge from tissue cysts, thus allowing for the establishment of

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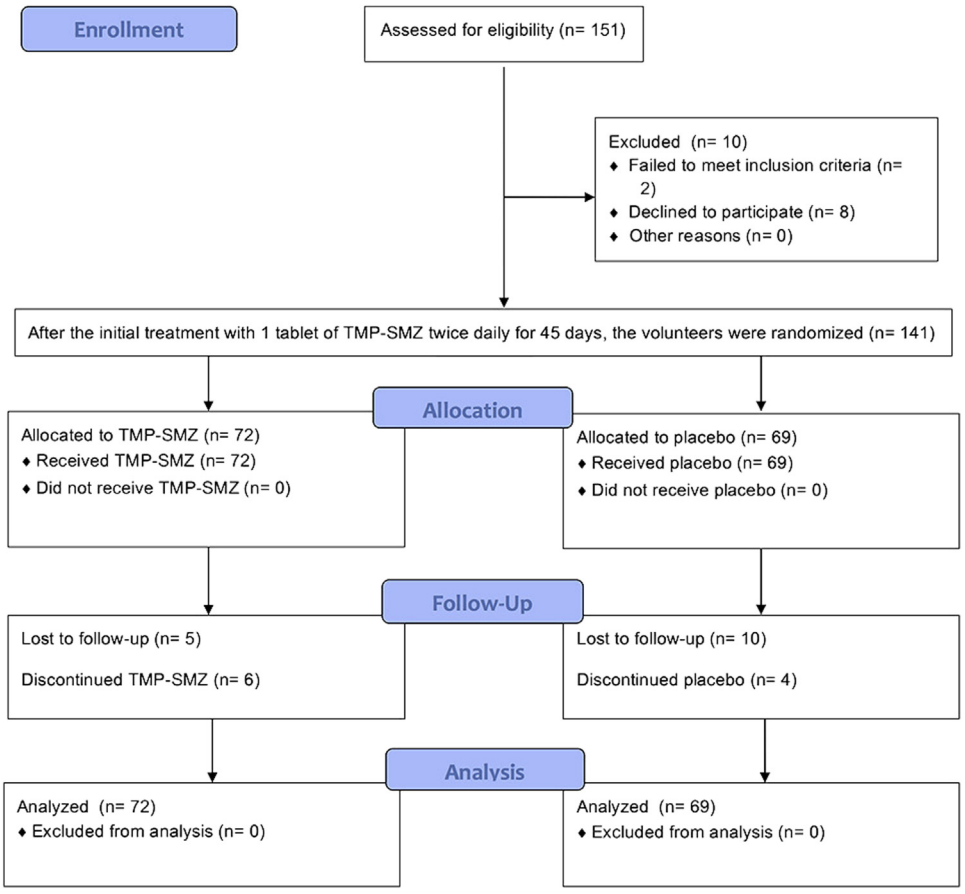

FIGURE 1. Trimethoprim-sulfamethoxazole (TMP-SMZ) vs placebo in reducing the risk of toxoplasmic retinochoroiditis recurrences: CONSORT flow diagram. After the initial treatment, the subjects were randomly assigned to Group 1 (1 TMP-SMZ tablet every 2 days for 311 days) or Group 2 (1 identical placebo tablet containing starch with no active ingredients every 2 days for 311 days). At the second- and third-year follow-up appointments, none of the subjects received treatment unless a new recurrence episode had occurred.

effective host control before the parasite can proliferate to an extent that causes clinically apparent lesions.[9,10]

An interesting report by Silveira and associates[8] with a 10-year follow-up period suggested that the prophylactic treatment effect disappears when the treatment is stopped; however, their results must be considered carefully. It was an open-label trial (non-placebo-controlled, nonmasked) with a loss of follow-up of 50%. This prophylactic treatment may provide good effects in a follow-up period shorter than 10 years,[11] though the former study was not able to detect this. This finding suggests the need for additional follow-up studies.

In our previous publication, 1 year of intermittent treatment with trimethoprim (160 mg)/sulfamethoxazole (800 mg) in the form of 1 tablet every 2 days reduced the rate of recurrent toxoplasmic retinochoroiditis.[11]

The purpose of this trial was to compare the effects of 1 year of treatment with TMP-SMZ vs placebo on reducing the risk of toxoplasmic retinochoroiditis recurrences in 3 years of follow-up after a recurrent episode.

METHODS

THIS STUDY WAS A SINGLE-CENTER, PROSPECTIVE, RANdomized, double-masked clinical trial. Ethics committee approval (institutional review board) was obtained, and all participants gave informed consent (National Bioethics Commission of Brazil Identifier No.: 0613.0.146.000-10). The trial was registered in October 2011 and began in November 2011 (Influence of Trimethoprim-Sulfamethoxazole on the Recurrence of Ocular Toxoplasmosis. Clinicaltrials.gov Identifier No.: NCT01449877; http://clinicaltrials.gov/show/NCT01449877).

The original manuscript (first report) included the first 100 subjects who completed the 1-year follow-up.[11] This cohort included all 151 subjects recruited from a uveitis clinic at a public hospital in Campinas, Brazil. The only incentive provided was free medication. The subjects were followed up for at least 36 months. The inclusion criterion was unilateral active recurrent toxoplasmic retinochoroiditis (defined as a new focal area of necrotizing

retinochoroiditis with active inflammation either adjacent to or remote from preexisting retinochoroidal scars, with IgG that was positive for toxoplasmosis). There were no IgM+ cases. Subjects who were under 18 years of age, were immunocompromised (eg, AIDS patients), were undergoing immunosuppressive treatments, or had concomitant retinochoroiditis from other causes (eg, tuberculosis) were excluded.

All subjects were treated for active toxoplasmic retinochoroiditis with 1 tablet of TMP-SMZ (160 mg/800 mg) twice daily for 45 days, and all lesions healed after this treatment (there were no subjects with unhealed lesions). Subsequently, 10 subjects dropped out of the study (Figure 1). The remaining subjects were randomly assigned to Group 1 (1 TMP-SMZ tablet every 2 days for 311 days) or to Group 2 (1 identical placebo tablet containing starch with no active ingredients every 2 days for 311 days). The regimen was chosen empirically based on a mix of 3 factors: the local experts' experience, patient compliance, and a previous report by Silveira and associates[10] regarding toxoplasmic retinochoroiditis prophylaxis. It was not based on pharmacokinetic data.

Randomization was 1:1. It 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 to the interventions in a masked fashion. Compliance with the drug regimen was evaluated by a count of the number of remaining tablets.

At the second-year and third-year follow-up appointments, the subjects did not receive treatment unless a new recurrence episode had occurred. Recurrences were treated with 1 tablet of TMP-SMZ (160 mg/800 mg) twice daily for 45 days. Patients were instructed to attend follow-up consultations every 3 months or when they experienced symptoms consistent with recurrent disease, such as redness, decreased vision, eye pain, and photophobia. Five patients in Group 1 and 10 patients in Group 2 missed their follow-up visits because they moved to other cities. Six patients in Group 1 and 4 patients in Group 2 discontinued interventions.

The trial was sponsored by the São Paulo State Research Foundation (FAPESP), Protocol No. 2010/15980-2. Trimethoprim/sulfamethoxazole tablets cost US $0.31 each and placebo tablets cost US $0.15 each.

Data were collected using a medical history form completed by the physician during the first medical examination. Best-corrected visual acuity (BCVA) based on ETDRS charts, as well as biomicroscopy, tonometry, indirect ophthalmoscopy with location of scars, recurrence of toxoplasmic retinochoroiditis, and medical events, were all recorded on a standardized form by a member of the medical staff in a masked fashion. Side effects were defined as any symptoms, signs, or biochemical abnormalities possibly related to treatment.

The primary outcomes were recurrent toxoplasmic retinochoroiditis within the first year of follow-up and recurrent toxoplasmic retinochoroiditis within the third year of follow-up.

TABLE 1. Demographic Data of Patients Treated With Trimethoprim-Sulfamethoxazole vs Placebo in Reducing the Risk of Toxoplasmic Retinochoroiditis Recurrences

	Patients Treated With TMP-SMZ (N = 72)	Patients Treated With Placebo (N = 69)	*P*
Age (y), mean (SD), median	32 (13), 33	33 (14), 33	.329[a]
Male-to-female ratio	36:36	30:39	.438[b]
Macular involvement/ peripheral involvement at study entry, n	22/50	24/45	.593[b]
Contralateral scars[c]	10	7	.495[b]

TMP-SMZ = trimethoprim-sulfamethoxazole.
[a]Mann-Whitney *U* test.
[b]χ^2 test.
[c]Scar in the contralateral eye.

Sample size calculations based on presumed recurrence rates of 0% in the treatment group and 15% in the placebo group 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 study was begun, 151 subjects were enrolled.

Descriptive statistics were calculated. Continuous data were expressed as the mean, median, and standard deviation (SD). 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. The probabilities of recurrence and of missing follow-up visits were assessed using the Kaplan-Meier survival analysis (log-rank test). Intention-to-treat analyses were conducted using SPSS, version 21 (IBM Corporation, Armonk, New York, USA). *P* values were 2-tailed. Statistical significance was set at .05.

RESULTS

BETWEEN AUGUST 24, 2011 AND FEBRUARY 1, 2013, 141 SUBjects were enrolled at a public hospital in Campinas, São Paulo State, Brazil and were randomized either to therapy using trimethoprim/sulfamethoxazole (72 subjects) or to placebo (69 subjects) (Figure 1). The mean age was 33 (SD 13) years, and 75 subjects (53.2%) were female. Age, sex distributions, lesion location, and the frequency of contralateral lesions were similar between the 2 groups (Table 1). The mean interval between the pre-enrollment recurrence episode and the recurrence observed during study follow-up was 263 (SD 219) days (median: 144 days).

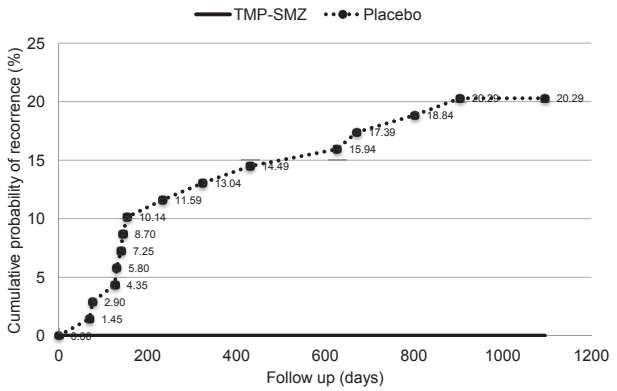

FIGURE 2. Kaplan-Meier plots of the probability of recurrence of toxoplasmic retinochoroiditis: graph of time to recurrence by treatment. TMP-SMZ = after prophylaxis with trimethoprim-sulfamethoxazole. All subjects were treated with 1 tablet of TMP-SMZ (160 mg/800 mg) twice daily for 45 days, and all lesions healed after this treatment. After this initial treatment, the subjects were randomly assigned to Group 1 (1 TMP-SMZ tablet every 2 days for 311 days) or Group 2 (1 identical placebo tablet containing starch with no active ingredients every 2 days for 311 days). At the second- and third-year follow-up appointments, none of the subjects received treatment unless a new recurrence episode had occurred.

The Kaplan-Meier survival analysis was used to compare missed follow-up visits between the 2 groups. No significant difference was found. The cumulative probability of missing follow-ups at 3 years was 14.5% (10/69) in the placebo group (mean follow-up of 984 days) and 6.9% (5/72) in the TMP-SMZ group (mean follow-up of 1046 days; $P = .139$, log-rank test).

Kaplan-Meier survival analysis was used to compare recurrence between the 2 groups (Figure 2). A significantly higher probability of recurrence was observed in the placebo group relative to the TMP-SMZ group. The cumulative probability of recurrence at 1, 2, and 3 years of follow-up was, respectively, 13.0% (9/69), 17.4% (12/69), and 20.3% (14/69) in the placebo group and 0% (0/72) in the TMP-SMZ group ($P < .001$, log-rank test). There were no cases of multiple recurrences in the same individual.

The mean changes in BCVA within 36 months were 22 (SD 20) letters (range −4 to 54) in the TMP-SMZ group and 22 (SD 18) letters (range −19 to 54) in the placebo group ($P = .768$, Table 2 and Figure 3).

Ten subjects—6 of whom (6/72; 8.3%) were from the TMP-SMZ group and 4 of whom (4/69; 5.8%) were from the placebo group ($P = .745$)—broke protocol (discontinued intervention after randomization), but no treatment-limiting toxicity or severe side effects were observed in either group. The reasons for discontinuation were not related to the intervention (reasons reported were poor compliance with pill treatment and/or difficulty following a routine). Three patients had mild epigastric burning pain: 2 (2/72; 2.8%) from the TMP-SMZ group and 1 (1/69; 1.4%) from the placebo group.

The data from the subjects with new toxoplasmic retinochoroiditis recurrence vs the remaining subjects in the placebo group are shown in Tables 3 and 4. New recurrences were more frequent among female subjects.

TABLE 2. Visual Acuity of Patients Treated With Trimethoprim-Sulfamethoxazole vs Placebo in Reducing the Risk of Toxoplasmic Retinochoroiditis Recurrences

	Patients Treated With TMP-SMZ (N = 72)	Patients Treated With Placebo (N = 69)	*P*
Baseline BCVA[b]	55 (SD 21) letters (20/80)	53 (SD 20) letters (20/100)	.151[a]
BCVA after 36 months[b]	78 (SD 18) letters (20/32)	74 (SD 19) letters (20/32)	.225[a]
Change in BCVA[c]	22 (SD 20) letters	22 (SD 18) letters	.136[a]

BCVA = best-corrected visual acuity (based on ETDRS charts); SD = standard deviation; TMP-SMZ = trimethoprim-sulfamethoxazole.

[a]Mann-Whitney *U* test.

[b]ETDRS letters and Snellen.

[c]Mean change in BCVA within 36 months.

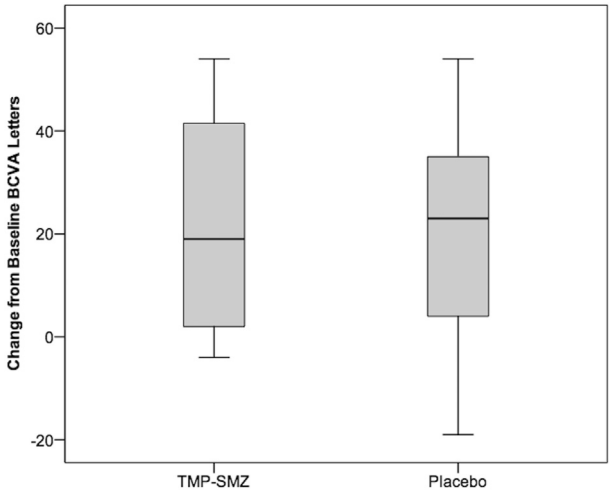

FIGURE 3. Trimethoprim-sulfamethoxazole (TMP-SMZ) vs placebo in reducing the risk of toxoplasmic retinochoroiditis recurrences: changes of best-corrected visual acuity (BCVA).

DISCUSSION

THE INCIDENCE OF RECURRENT TOXOPLASMIC RETINOchoroiditis was significantly higher in subjects treated with placebo than in subjects who received 1 TMP-SMZ tablet every 2 days for 1 year.

TABLE 3. Demographic Data of the Patients With New Recurrence of Toxoplasmic Retinochoroiditis vs Remaining Patients in the Placebo Group

	New Recurrence (N = 14)	No Recurrence (N = 55)	*P*
Age (y), mean (SD), median	32 (11), 32	34 (15), 33	.228[a]
Male-to-female ratio	2:12	28:27	.016[b]
Macular involvement/ peripheral involvement at study entry	5/9	19/36	.935[b]
Contralateral scars[d]	2	12	.624[c]

SD = standard deviation.
[a]Mann-Whitney *U* test.
[b]χ^2 test.
[c]Fisher exact test.
[d]Scar in the contralateral eye.

TABLE 4. Visual Acuity of the Patients With New Recurrence of Toxoplasmic Retinochoroiditis vs Remaining Patients in the Placebo Group

	New Recurrence (N = 14)	No Recurrence (N = 55)	*P*
Baseline BCVA[b]	45 (SD 16) letters (20/125)	56 (SD 20) letters (20/80)	.115[a]
BCVA after 36 months[b]	72 (SD 19) letters (20/40)	75 (SD 19) letters (20/32)	.965[a]
Change in BCVA[c]	27 (SD 19) letters	20 (SD 17) letters	.747[a]

BCVA = best-corrected visual acuity (based on ETDRS charts); SD = standard deviation.
[a]Mann-Whitney *U* test.
[b]ETDRS letters and Snellen.
[c]Mean change in BCVA within 36 months.

The initially active toxoplasmosis lesions were successfully treated in all cases in which TMP-SMZ was taken twice daily for 45 days. Soheilian and associates[12] compared the efficacy of the classic treatment for ocular toxoplasmosis (pyrimethamine, sulfadiazine, and prednisolone) to a regimen consisting of TMP-SMZ plus prednisolone. The authors observed that active toxoplasmosis retinochoroiditis was resolved in all patients with more than 6 weeks of treatment. Opremcak and associates[13] also concluded that all patients treated with TMP-SMZ for ocular toxoplasmosis experienced resolution of active retinochoroiditis. Trimethoprim-sulfamethoxazole is readily available as a fixed-combination antibiotic and has been shown to be relatively safe. It offers the advantage of increased patient compliance as a result of easier dosing (1 tablet orally twice a day). Studies are needed on the use of TMP-SMZ after an initial remission attributed to other antitoxoplasmosis drugs.

In an outbreak of systemic toxoplasmosis in British Columbia in 1995, 4 out of 20 patients (20%) who presented with ocular toxoplasmosis developed recurrences during a follow-up period of 13–61 weeks.[14] Bosch-Driessen described that the risk of recurrences within 2 years in cases of postnatally acquired ocular toxoplasmosis is 57%.[4] Garweg and associates reported recurrence in approximately 4 out of 5 patients, a rate that was higher 2 years after the first episode.[15] The frequency of recurrences in our subjects treated with placebo differed from the rate of recurrence reported in these other studies; however, this difference may be attributable to the small sample sizes used in previous studies. Sample size could, in fact, be one example of the potential problem with generalizability; it demonstrates the need to conduct confirmatory studies in different settings. Holland and associates confirmed that the risk of recurrence was highest immediately after an episode of active disease and that recurrence had a tendency to occur in clusters.[16]

The majority of the new recurrences (64.3%) occurred within the first year (21.4% in the second year and 14.3% in the third year). Even so, it was not possible to determine whether a longer (>1 year) prophylactic treatment would offer additional benefits, because no recurrence occurred in the treated group. A longer follow-up period would be necessary to answer this question, but the present results encourage a 1-year prophylactic protocol. A recent report by Silveira and associates[8] with a 10-year follow-up period suggested that the prophylactic treatment effect disappears when the treatment is stopped; however, their results must be considered carefully. It was an open-label trial (non-placebo-controlled, nonmasked) with a loss of follow-up of 50%.

A possible disease mechanism in recurrent lesions is an inflammatory reaction to parasite antigens, either in response to antigens released as a result of tissue cyst breakdown (though without parasite reactivation and proliferation) or during very brief periods of parasite proliferation, before host defenses drive the parasites back into tissue encystment.[17] The TMP-SMZ combination may act upon one of these mechanisms in the first year after recurrence (after lesions are healed), a factor that suggests its effect in further long-time therapy. Further studies are necessary to clarify the duration of the effects of the drug on recurrence, as well as to determine the mechanism for the prolonged time of effect. Perhaps a hypothesis to explain the additional protection in the 2 years after cessation of the prophylactic treatment would be that the most viable cysts tend to erupt in the first months after the initial infection.

Some questions remain unanswered. Recurrence of toxoplasmic retinochoroiditis has been found to be more common in women. Wira and Fahey[18] hypothesized that there is a window of vulnerability in a normal menstrual cycle (7–10 days following ovulation). During that period, aspects of the innate, humoral, and cell-mediated immune

systems are suppressed by sex hormones to optimize conditions for reproduction. In contrast to this aspect, Braakenburg and associates[17] found that recurrence rates of ocular toxoplasmosis are not higher during pregnancy, a situation in which these hormonal alterations occur. We suggest that further confirmatory studies conducted on women take this factor into account during follow-up evaluations.

Although the intermittent treatment used in this study was not found to benefit final BCVA, toxoplasmic retinochoroiditis is the most prevalent cause of infectious posterior uveitis and recurrent episodes seem likely to take a toll on vision. In many cases, the inflammatory reaction is severe. Scar tissue results from retinal and choroidal necrosis. With reactivation of the cysts located at the border of the scars, the areas of newly active necrotizing retinitis are usually adjacent to old scars. This is especially relevant if the previous lesion is near the macula.[1] Even though visual acuity was not lost in the short period of this study, Holland and associates have shown vision loss to occur in some patients who experience repeated recurrences.[16]

Antibiotics used for long-term prophylactic treatment of toxoplasmic retinochoroiditis must be safe and well tolerated. Prolonged treatment may be associated with side effects. However, in our study, no treatment-limiting toxicity or adverse effects were observed. It is important to reiterate that the reason for some patients' discontinuation was not related to the intervention. Therefore, in patients who initially tolerate a high dose of TMP-SMZ, prolonged treatment for 12 months seems to be safe. The physician must be alert to hematologic, renal, or hepatic side effects. The combination of trimethoprim-sulfamethoxazole is generally well tolerated, with few patients experiencing side effects. The most frequent are gastrointestinal disturbances and allergic skin reactions; however, severe reactions, although rare, have been reported, including Stevens-Johnson syndrome and blood dyscrasias.[19–22] One potential disadvantage of chronic treatment is the potential for drug resistance after prolonged exposure, according to a report by Doliwa and associates.[23]

In a recent editorial, Grigg and associates[24] recommended that secondary prophylaxis to prevent disease recurrence in high-risk patients be the standard treatment worldwide. In the present study, the 3-year cumulative incidence of recurrent toxoplasmic retinochoroiditis was significantly higher in subjects treated with placebo compared to subjects who received 1 TMP-SMZ tablet every 2 days for 1 year, even 2 years after discontinuing the prophylactic treatment. These results confirm the usefulness of this treatment and suggest that TMP-SMZ may be used safely in select cases for prophylaxis of recurrent toxoplasmic retinochoroiditis. In conclusion, there is level I evidence that intermittent use of TMP-SMZ following an active episode of ocular toxoplasmosis significantly reduces the risk of recurrence for at least 3 years after the active episode. This evidence introduces an important paradigm regarding the benefits of prophylactic treatment of this disease.

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