

Prospective Randomized Trial of Trimethoprim/Sulfamethoxazole versus Pyrimethamine and Sulfadiazine in the Treatment of Ocular Toxoplasmosis

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Objective: To compare the efficacy of the classic treatment of ocular toxoplasmosis (pyrimethamine, sulfadiazine, and prednisolone) with a regimen consisting of trimethoprim/sulfamethoxazole (co-trimoxazole) plus prednisolone.

Design: Prospective randomized single-blind clinical trial.

Participants: Fifty-nine patients with active ocular toxoplasmosis were randomly assigned to 2 treatment groups: 29 were treated with pyrimethamine/sulfadiazine, and 30 patients received trimethoprim/sulfamethoxazole.

Intervention: Treatment consisted of 6 weeks' treatment with antibiotics plus steroids. Antitoxoplasmosis antibodies (immunoglobulin M [IgM] and IgG) were measured using an enzyme-linked immunosorbent assay.

Main Outcome Measures: Changes in retinochoroidal lesion size after 6 weeks' treatment, visual acuity (VA) before and after intervention, adverse drug reactions during follow-up, and rate of recurrence.

Results: Active toxoplasmosis retinochoroiditis resolved in all patients over 6 weeks' treatment, with no significant difference in mean reduction of retinochoroidal lesion size between the 2 treatment groups (61% reduction in the classic treatment group and 59% in the trimethoprim/sulfamethoxazole group, $P = 0.75$). Similarly, no significant difference was found in VA after treatment between the 2 groups (mean VAs after treatment were 0.12 logarithm of the minimum angle of resolution [logMAR] [20/25] in the classic treatment group and 0.09 logMAR [20/25] in the trimethoprim/sulfamethoxazole group, $P = 0.56$). Adverse effects were similar in both groups, with one patient in each suffering from any significant drug side effects. The overall recurrence rate after 24 months' follow-up was 10.16%, with no significant difference between the treatment groups ($P = 0.64$).

Conclusions: Drug efficacies in terms of reduction in retinal lesion size and improvement in VA were similar in a regimen of trimethoprim/sulfamethoxazole and the classic treatment of ocular toxoplasmosis with pyrimethamine and sulfadiazine. Therapy with trimethoprim/sulfamethoxazole seems to be an acceptable alternative for the treatment of ocular toxoplasmosis. *Ophthalmology* 2005;112:1876-1882 © 2005 by the American Academy of Ophthalmology.

Ocular toxoplasmosis is caused by the intracellular parasite *Toxoplasma gondii* and is a major cause of preventable blindness, particularly in young people.^{1,2} It accounts for 15% to 17% of all cases of uveitis, 25% of posterior uveitis in the United States, and >85% of posterior uveitis in Brazil.¹ In a previous study conducted at our institution,

toxoplasmosis was identified as the most common cause of posterior uveitis, accounting for 54.5% of cases.³

The goal of treatment is to arrest the multiplication of the parasite during the period of active retinochoroiditis to prevent irreversible damage to the retina and optic nerve.^{4,5} Currently, the most common treatment of choice consists of pyrimethamine and sulfadiazine plus corticosteroids, aimed at controlling the reactivation of parasites from dormant

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cysts and the associated inflammatory reaction. The cost of this classic treatment has been great, with significant adverse side effects; pyrimethamine administration requires weekly monitoring of blood cell count and platelets and coadministration of folinic acid for guarding against leukopenia and thrombocytopenia.^{1,2,4,6} In addition, these drugs are not readily available in some areas,⁶ and compliance is difficult, given that the patient needs to take up to 10 pills per day. Other available treatments include quadruple drug therapy (classic treatment plus clindamycin), clindamycin, trimethoprim/sulfamethoxazole, spiramycin, minocycline, azithromycin, atovaquone, and intravitreal injection of clindamycin and dexamethasone.^{1,2,4,6-13} Further study into a safer and simpler treatment for toxoplasmosis is warranted, given that most current treatments are not free of significant toxicity.^{2,6}

Treatment of ocular toxoplasmosis with trimethoprim/sulfamethoxazole is a treatment option,^{1,2,4,6,11,14} but no randomized controlled study has specifically compared this regimen with classic therapy. Trimethoprim/sulfamethoxazole therapy works like the combination of pyrimethamine and sulfadiazine, which is mediated through inhibition of sequential steps in the synthesis of tetrahydrofolic acid, an essential precursor of purines and DNA. Both laboratory and clinical studies have established the efficacy of toxoplasmosis treatment with trimethoprim/sulfamethoxazole.^{6,15} The use of trimethoprim/sulfamethoxazole has gained popularity among uveitis specialists, such that the use of this drug regimen from 1991 to 2002 rose from 5% to 28%.^{7,8} Trimethoprim/sulfamethoxazole has been used for prophylaxis of toxoplasmosis encephalitis in AIDS patients, which may explain why it has similarly become a favorable option with ophthalmologists.^{2,16} More recently, trimethoprim/sulfamethoxazole prophylaxis has shown efficacy in preventing recurrence of ocular toxoplasmosis.¹⁷ Trimethoprim/sulfamethoxazole is less toxic to hematopoiesis and eliminates the need for folinic acid supplementation as well as hematologic evaluation, except in patients with renal failure or advanced age. It is a relatively inexpensive and readily obtainable drug that is also available in a liquid formula for pediatric patients.

In this study, we compare the efficacy of trimethoprim/sulfamethoxazole with that of classic therapy in ocular toxoplasmosis.

Patients and Methods

This study was conducted in a controlled, randomized, single-blind fashion. Patients were diagnosed clinically with ocular toxoplasmosis, as defined by the presence of visual complaints and an area of focal necrotizing retinochoroidal lesion appearing as a whitish-yellow region with a blurred margin plus or minus the accompaniment of an old lesion.^{1,4,18-20} The following were used as inclusion criteria:

1. Location of lesion within zone 1 of the retina (region extending 3000 μm from the foveal center)⁷ or a lesion >2 disc diameters in size with 3 to 4+ vitreous inflammation within zones 2 or 3. (Zone 2 is defined as the region extending anteriorly from the border of zone 1 to the equator, and zone 3 is defined

as the region from the border of zone 2 to the ora serrata.⁷)

2. Presence of retinal lesion at least 500 μm outside the center of the macula.
3. Lack of history of allergic reaction to the drugs used in this study.
4. Lack of any other ocular disease.

Criteria used to exclude patients from the study included (1) visual acuity (VA) of <20/200 in the fellow eye, (2) location of the lesion within the center (500 μm) of the macula, (3) development of allergic reaction to the medication, (4) leukopenia (white blood cell count < 5000) or platelet count < 120 000/ml, and (5) lesions smaller than 2 disc diameters in zones 2 and 3.^{4,18}

Patients were recruited from the Labbafinejad Medical Center Uveitis Clinic in Tehran, Iran from January 2000 to the end of February 2004. Patients consented to participation in the study, and it was approved by the ethics committees of the hospital and the Shaheed Beheshti University of Medical Sciences. Of the 71 patients enrolled in the study, 59 (36 men, 23 women) completed follow-up. Twenty-nine patients were treated with the classic regimen consisting of pyrimethamine and sulfadiazine, and 30 were treated with trimethoprim/sulfamethoxazole. Classic treatment consisted of an initial dose of 100 mg of pyrimethamine daily for 2 days, followed by a 25-mg dose daily, 2 g of sulfadiazine daily for 2 days followed by 500-mg dosing every 6 hours, and 5 mg of folinic acid daily. In the second group, treatment consisted of 2 tablets of trimethoprim (80 mg)/sulfamethoxazole (400 mg) every 12 hours. In both groups, treatment was continued for 6 weeks; oral prednisolone was administered at 1 mg/kg daily starting from the third day of therapy, and the dose was tapered over 2 weeks.

Response to treatment was identified as sharpening of the lesion border with or without hyperpigmentation and resolution of vitreous inflammation.^{1,4,18,19} Recurrence was defined as the appearance of an active lesion adjacent to an old scar or elsewhere.⁴ Patients were examined by an ophthalmologist on day 1, at the end of weeks 1 through 6, and every 3 months. All patients underwent measurement of VA and anterior vitreous inflammation according to the system devised by Kanski²¹ and Kimura et al.²² Fundus examination at the slit lamp with a 90-diopter lens and indirect ophthalmoscopy were undertaken in every patient. Lesion size was measured in millimeters on fundus photography, and the percentage of reduction in size was calculated based on the greatest length diameter of the lesion. Fundus photographs on day 1 and week 6 of therapy were read independently by 2 masked retina specialists. Serum measurements of immunoglobulin G (IgG) and IgM anti-toxoplasmosis antibodies (enzyme-linked immunosorbent assay) were obtained once in all cases; weekly complete blood cell and platelet counts were performed in patients on the classic treatment regimen. Patients were observed after completion of treatment for at least 24 months. Lesion size reduction was considered as the primary outcome measure, and VA, vitreous inflammation, adverse drug reaction, and recurrence rate were secondary outcome measures.

Sample Size, Randomization Scheme, and Masking Procedure

Type I (α) and type II (β) errors were set at 0.05 and 0.2, respectively. Twenty percent lesion size reduction was considered a significant intergroup difference. Regarding the above and allowance for 30% patient loss during 24 months' follow-up, a sample size of 35 patients in each group was calculated.

Randomization was performed by dividing all cases into 12

equal blocks. Each block contained 6 patients, who were allocated into the 2 treatment groups using randomization tables.

At each follow-up examination, an unmasked ophthalmologist (M-MS) completed the physical examination, including VA measurement, slit-lamp examination, tonometry, funduscopy, and evaluation of laboratory tests, and then the patient consulted with a masked retina specialist (MS) for measuring the clinical outcomes of the study, such as determining lesion sharpening based on the change in lesion color, development of pigmentation, and amount of vitreous inflammation. Fundus photographs were evaluated by 2 independent masked observers (MS, MHD).

To maintain patient masking, all medications were packaged similarly and labeled by number: 1 (the classic regimen) and 2 (trimethoprim/sulfamethoxazole). Instruction for use was given by the same unmasked physician (M-MS).

Statistical Methods

An independent-sample *t* test was performed to compare age, lesion size reduction, and VA before and after treatment between groups. The chi-square test was employed to compare gender distribution, vitreous inflammation before and after treatment, and recurrence rate between groups. A paired *t* test was also used to compare VA and lesion size before and after treatment. A McNemar test was performed to compare vitreous inflammation before and after treatment in each group. *P* values of <0.05 were considered significant.

Results

Of 71 patients initially recruited, 35 were randomly assigned to receive classic therapy, and 36 to treatment with trimethoprim/sulfamethoxazole. Six patients in the trimethoprim/sulfamethoxazole group (1 due to development of drug allergy and 5 due to incomplete follow-up) and 6 patients in the classic treatment group (1 due to development of allergic reaction to sulfadiazine and 5 due to incomplete follow-up) were not included in the final analysis. The classic therapy group consisted of 18 men (62.1%) and 11 women (37.9%), and similarly, the trimethoprim/sulfamethoxazole group consisted of 18 men (60%) and 12 women (40%) (*P* = 0.54). Mean ages in the classic therapy group and trimethoprim/

sulfamethoxazole group, respectively, were 23.5 ± 7.4 years (range, 12–45) and 26.6 ± 11.7 years (range, 12–59) (*P* = 0.23). There was no significant difference between the 2 groups with regard to age, gender, and VA before treatment (Table 1). Durations of follow-up were similar, with means of 33 ± 4 months (range, 24–39) in the classic group and 31.5 ± 4.5 months (range, 24–40) in the trimethoprim/sulfamethoxazole treatment group.

The treatment groups responded similarly to treatment with improved VA. Mean VAs before treatment were 0.68 logarithm of the minimum angle of resolution (logMAR) (20/100 [range, 20/20–counting fingers [CF] at 40 cm]) in the classic therapy group and 0.57 logMAR (20/80 [range, 20/20–CF at 40 cm]) in the trimethoprim/sulfamethoxazole group (*P* = 0.52) (Table 1). Mean VAs achieved after treatment were 0.12 logMAR (20/25 [range, 20/20–20/200]) in the classic therapy group and 0.09 logMAR (20/25 [range, 20/20–20/160]) in the trimethoprim/sulfamethoxazole group, with no significant difference between groups (*P* = 0.56). Within each group, there was significant improvement in VA after treatment; VA increased by 0.56 logMAR units (5.5 lines) in the classic therapy group (*P* < 0.01) and by 0.52 logMAR units (5 lines) in the trimethoprim/sulfamethoxazole group (*P* < 0.01). However, there was no statistically significant difference in visual improvement between the 2 treatment groups (*P* = 0.75) (Fig 1).

Visual acuity improved in all cases after treatment, except for 1 patient in each group who had full VA (20/20) before intervention. Twenty-four cases (82.8%) in the classic treatment group and 27 cases (90%) in the trimethoprim/sulfamethoxazole group achieved VA of 20/40 or better (Table 2). Overall, 16 cases with initial VA of 20/50 to 20/200 in both groups attained VA of 20/40 or better. In 5 patients (3 in the classic group and 2 in the trimethoprim/sulfamethoxazole group) of 13 cases with initial VA of <20/200, vision improved to 20/40 or better; the 8 remaining cases (5 in the classic group and 3 in the trimethoprim/sulfamethoxazole group) finally achieved VA of 20/50 to 20/200 (Table 2). No statistically significant intergroup difference was observed in time required to achieve best posttreatment VA (Table 1).

Of the 59 patients in the study, we were able to measure retinal lesion size in 49. Five patients in the classic therapy group (1 individual due to media opacity and 4 due to failure to obtain a second fundus photograph) and 5 patients in the trimethoprim/sulfamethoxazole group (2 individuals due to media opacity, 1 due

Table 1. Patient Characteristics before and after Treatment (n = 59)

	Classic Treatment Group (n = 29)	Trimethoprim/Sulfamethoxazole Treatment Group (n = 30)	P Value
Male	18 (62.1%)	18 (60%)	0.54
Female	11 (37.9%)	12 (40%)	
Age (yrs)	23.5 ± 7.4 (range, 12–45)	26.6 ± 11.7 (range, 12–59)	0.23
Follow-up (mos)	33 ± 4	31.5 ± 4.5	0.17
Presence of previous retinal scar	15 (51.7%)	14 (46.7%)	0.44
Visual acuity before treatment	0.68 logMAR (20/100)	0.57 logMAR (20/80)	0.69
Visual acuity after treatment	0.12 logMAR (20/25)	0.09 logMAR (20/25)	0.56
Improvement in visual acuity	0.56 logMAR, 5.5 Snellen lines	0.52 logMAR, 5 Snellen lines	0.75
Reduction of vitreous inflammatory cells (0–trace cells) 6 wks after treatment	20 (69%)	17 (56.7%)	0.24
Positive IgG titer	29 (100%)	30 (100%)	1
Positive IgM titer	13 (44.8%)	9 (30%)	0.18
Recurrence during 24 mos after treatment	3 (10.3%)	3 (10%)	0.64
Adverse drug reaction	1 (2.9%)	1 (2.8%)	0.98
Time to achieve best visual acuity (days)	35.4 ± 5.6	32.8 ± 5.8	0.09

IgG = immunoglobulin G; logMAR = logarithm of the minimum angle of resolution.

to lack of initial fundus photography, and 2 others due to unavailability of a second fundus photograph) were excluded from this outcome measure. There was no significant difference between the 2 treatment groups in terms of reduction in retinal lesion size; patients in the classic therapy group had a mean reduction in lesion size of 61% (range, 10%–100%), and patients in the trimethoprim/sulfamethoxazole group demonstrated a mean reduction of 59% (range, 10%–100%) after 6 weeks of treatment ($P = 0.75$).

There was also an insignificant difference in reduction of vitreous inflammation between groups, with 20 patients (69%) in the classic therapy group and 17 patients (56.7%) in the trimethoprim/sulfamethoxazole group showing trace to no inflammatory cells after treatment ($P = 0.24$).

In 29 patients (49.2%), a previous retinal scar was detected; of these, 15 (51.7%) were assigned to classic therapy and 14 (46.7%) were in the trimethoprim/sulfamethoxazole group ($P = 0.44$).

Antitoxoplasmosis antibody analysis revealed positive IgG titers in all patients in both treatment groups. Immunoglobulin M titers were positive in 13 (44.8%) and 9 (30%) cases in the classic and trimethoprim/sulfamethoxazole groups, respectively ($P = 0.18$). Immunoglobulin M–positive and IgM–negative cases responded similarly to both treatment regimens in terms of retinal lesion size reduction (Table 3).

During the follow-up period, a total of 6 recurrences occurred in the patient population, of which 3 (10.3%) were observed in the classic therapy group and 3 (10%) in the trimethoprim/sulfamethoxazole group ($P = 0.64$). In the classic treatment group, 1 patient had 3 recurrence episodes 2, 3, and 7 months after the first, second, and third treatment courses, respectively. The 2 other patients had 2 episodes of recurrence 11 and 12 months after initial treatment, followed by a second episode 6 and 7 months after retreatment. In the trimethoprim/sulfamethoxazole group, 1 patient experienced 2 recurrence episodes, both of which occurred 2 months after initial therapy and retreatment. The other 2 cases had a single recurrence episode 8 and 10 months after initial therapy. Mean times from treatment to the first recurrence in the classic and trimethoprim/sulfamethoxazole groups (8.3 ± 5.5 vs. 6.6 ± 4.1 months, respectively) did not differ significantly.

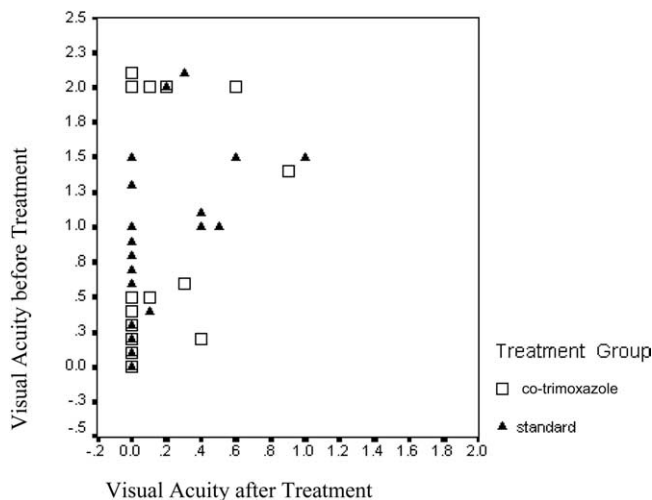


Figure 1. Scattergram of pretreatment and posttreatment visual acuity demonstrates almost equal improvement in classic treatment and trimethoprim/sulfamethoxazole (co-trimoxazole) treatment groups. The decrease in total number of symbols reflects overlapping symbols indicating the same level of vision in each group (15 overlapped symbols in the trimethoprim/sulfamethoxazole treatment group and 10 overlapped symbols in the classic treatment group).

Table 2. Visual Acuity

	Before		After	
	Classic	TMP/SMX	Classic	TMP/SMX
20/20–20/40 (%)	12 (41.4)	18 (60)	24 (82.8)	27 (90)
20/50–20/200 (%)	10 (34.5)	6 (20)	5 (17.2)	3 (10)
<200 (%)	7 (24.1)	6 (10)	0 (0)	0 (0)
Total (%)	29 (100)	30 (100)	29 (100)	30 (100)

TMP/SMX = trimethoprim/sulfamethoxazole.

Adverse drug reactions were limited to 1 patient (2.9%) in the classic therapy group and 1 patient (2.8%) receiving the trimethoprim/sulfamethoxazole regimen; in both cases, the drug reaction was development of a rash. Both patients were taken off their respective medication regimens and excluded from the study.

Retrospective Power Calculations

For the purpose of performing retrospective power calculation, lesion size reduction after treatment was defined as the main outcome measure. Post hoc power analysis was performed using SPSS (version 11.5, SPSS Inc., Chicago, IL). Forty-nine cases with adequate media clarity and fundus photographs with acceptable quality were used to evaluate the power of this study. Abilities to detect intergroup differences in lesion size reduction of 30%, 20%, 10%, and 2.25% (which was the observed intergroup difference in this study) were calculated with α set at 0.05.

Post hoc power analysis revealed that our study had 80% power to detect a 20% difference in lesion size reduction between treatment groups. Sample sizes required to detect differences of 10% and the observed 2.25% with similar power would have been 94 and 1860 cases, respectively, in each treatment group.

Discussion

Our study revealed no significant difference between classic treatment with pyrimethamine and sulfadiazine and trimethoprim/sulfamethoxazole for ocular toxoplasmosis retinochoroiditis in terms of reduction in lesion size. Mean reductions in size of retinal lesions were 61% in the classic therapy group and 59% in the trimethoprim/sulfamethoxazole group. In a similar prospective multicenter study by Rothova et al,² a significant reduction in retinal lesion (defined as at least half a disc diameter reduction in diameter) was found in 49% of patients receiving classic therapy and 11% of patients receiving trimethoprim/sulfamethoxazole. Given the use of disc diameter to measure reduction in lesion size in this study, measurement of initial retinal lesions was limited to those greater than half a disc diameter in size. However, we evaluated response to treatment by the percentage of decrease in the size of the initial lesion. Moreover, Rothova et al used a 4-week period of treatment, whereas our patients were treated for 6 weeks. There is also a difference in the treatment regimen between the 2 studies, with Rothova et al utilizing a 960-mg dose of trimethoprim/sulfamethoxazole twice daily during the first 2 weeks and then 380 mg 2 times a day for the last 2 weeks, whereas in our study we continued the initial 960-mg dose for the entire

Table 3. Percentage of Lesion Size Reduction (n = 49)

	IgM-Positive Patients [% (n)]	IgM-Negative Patients [% (n)]	P Value
Classic treatment group	72±19.9 (10)	50±29.9 (14)	0.055
TMP/SMX treatment group	52.1±23.8 (7)	61.6±17.8 (18)	0.285
Total no. of patients	17	32	

IgM = immunoglobulin M; TMP/SMX = trimethoprim/sulfamethoxazole.

6 weeks of treatment. As such, it is likely that the higher dose and longer duration of trimethoprim/sulfamethoxazole treatment in our study caused the greater response.

Response to treatment measured by change in VA revealed a nonsignificant difference between the treatment groups, with a 0.56-logMAR (5.5 lines of vision) improvement in acuity in the classic therapy group and 0.52-logMAR (5 lines of vision) improvement in patients receiving trimethoprim/sulfamethoxazole. In a study by Opremcak et al,⁶ mean VA after treatment in patients receiving trimethoprim/sulfamethoxazole was 20/30, with an improvement of 4.6 lines, which is consistent with our findings. Similarly, in Rothova et al's study,² which utilized 3 different treatment regimens, including classic and trimethoprim/sulfamethoxazole, there was no significant difference in improvement in VA between the study groups after treatment. In a retrospective study of 154 patients with active uveitis, Bosch-Driessen et al¹³ also found no significant difference in VA between patients receiving different treatment regimens at the conclusion of therapy. Nevertheless, measuring the effect of treatment on VA is difficult to assess, given the importance of lesion location and severity of inflammation in the active phase of toxoplasmosis. Therefore, reduction in lesion size and inflammatory signs may be a more objective means of comparison.

We also found a comparable effect in terms of inflammatory response in both treatment groups. After 6 weeks of therapy, there was resolution of signs of vitreous inflammation in 69% of patients receiving classic therapy and 56.7% of patients on trimethoprim/sulfamethoxazole. Bosch-Driessen et al¹³ reported resolution of vitreous inflammation in 71% of their patients after 4 weeks of treatment with classic therapy.

No previous retinal scar was noted in 50.8% of patients in our study. Two previous studies reported 31% and 40% of their patients without previous retinal scars.^{2,13} The greater proportion of patients without a previous scar in our study may reflect the prevalence of acquired versus congenital cases in Iran. The finding that 37% of our patients had positive IgM titers may be supportive evidence for an acquired etiology; there is increasing evidence that an acquired infection may be more common than once thought.^{23,24}

There were 6 cases of recurrence (10.16%) in our entire patient population with an average follow-up of 32.3 months, with no significant difference between treatment groups. In Rothova et al's study,² the rate of recurrence after 1 year was 2.7%, with a mean of 41% after 2 years'

follow-up, and no particular treatment regimen was found to be superior in preventing recurrences. Opremcak et al⁶ found only 1 case of recurrence (6.25%) in their patient population after 10 months' follow-up, whereas in another study, Bosch-Driessen and Rothova reported a 29% rate of recurrence within 1 year after treatment.²⁵ An even higher rate of recurrence (56%) within 1 year was reported by Bosch-Driessen et al⁹ in a population of patients receiving classic therapy with pyrimethamine and sulfadiazine. As evident, the rate of recurrence varies greatly, as reported by different researchers, and correlates positively with the period of follow-up. Other factors that may play a major role in recurrence include host factors as well as the pathogenicity of the organism.

In our study, we found no significant difference in adverse drug reactions between treatment groups, which were limited to 1 case (3.4%) in the classic therapy group and 1 patient (3.3%) receiving trimethoprim/sulfamethoxazole. Similar to other published studies, these adverse reactions resolved with withdrawal of treatment.^{2,6} In Rothova et al's study,² the rate of adverse drug reactions in patients receiving trimethoprim/sulfamethoxazole was only 4%, whereas 26% of patients receiving classic therapy had an adverse drug reaction. Another study reported an adverse drug reaction in 64% of patients receiving classic therapy with pyrimethamine and sulfadiazine.⁹ The different rates of adverse drug reactions may have been due to the minimal therapeutic dose (25 mg of pyrimethamine daily and 2 g of sulfadiazine daily) utilized in patients receiving classic therapy in our series. Moreover, studies with greater sample sizes are required to demonstrate the true incidence of such events.

The decision to pursue trimethoprim/sulfamethoxazole as a drug regimen alternative to classic treatment with pyrimethamine and sulfadiazine in this study was multifaceted. First, since the appearance of Opremcak et al's 1991 study⁶ comparing the efficacy of 2 different trimethoprim/sulfamethoxazole regimens for ocular toxoplasmosis, there seems to be increasing acceptance of this drug regimen by uveitis specialists, its use rising from 5% in 1991 to 28% in 2002.⁷ Moreover, from a theoretical perspective trimethoprim/sulfamethoxazole is a logical treatment choice because this combination drug acts in a fashion similar to that of pyrimethamine and sulfadiazine in inhibiting synthesis of tetrahydrofolic acid, and its efficacy against *Toxoplasma gondii* has been established in vitro.¹⁵

In a recent survey of current practices in the management of ocular toxoplasmosis, a total of 24 different treatment regimens were described. In addition to trimethoprim/sulfamethoxazole, competing alternative treatments to classic therapy include clindamycin, macrolides (azithromycin and spiramycin), allopurinol, and atovaquone.⁷ Clindamycin, although effective in the treatment of ocular toxoplasmosis, is an antibiotic highly associated with the development of pseudomembranous colitis from *Clostridium difficile*, manifesting as limited diarrhea to fatal toxic megacolon.^{26,27} The macrolide antibiotic azithromycin, which has a relatively safer drug profile, with fewer side effects, has been shown to be as effective as classic treatment only when used in combination with pyrimethamine.⁹ A smaller study dem-

onstrating azithromycin's efficacy failed to compare it with classic therapy.²⁸ However, another study that compared spiramycin with classic treatment found monotherapy with spiramycin to be superior in terms of reduction of active disease duration and side effects.²⁹ A recent unpublished paper has offered hope in the use of allopurinol as an antiinflammatory treatment (Adam HI, et al. Allopurinol as an anti-inflammatory treatment in ocular toxoplasmosis. Presented at: Deutsche Ophthalmologische Gesellschaft 98th annual meeting, September, 2000; Berlin, Germany); yet, this study did not compare allopurinol with the classic regimen. Another agent, atovaquone (hydroxynaphthoquinone), has been used effectively in treatment of active disease and shown to be relatively safe in terms of side effects,³⁰ but this regimen also was not compared with classic treatment, and its use seems to be limited by cost as well as lack of clinical experience.

The results of this study demonstrated trimethoprim/sulfamethoxazole to be as effective as classic treatment for toxoplasmosis retinochoroiditis; this finding is substantiated by similar clinical studies with trimethoprim/sulfamethoxazole.⁶ Although one study found a smaller reduction in lesion size in patients on trimethoprim/sulfamethoxazole when compared with classic treatment and no treatment, there was a trend toward shorter duration of inflammatory activity with trimethoprim/sulfamethoxazole.² Our findings are strengthened by the randomized and controlled nature of this study, and by the relatively large number of patients in each treatment group. Potential weaknesses include our inability to mask evaluating physicians completely to the patients' assigned treatment regimen and the inability to obtain fundus photographs in some of our patients. Nevertheless, the positive response to treatment is not likely to have been significantly altered, as all 3 measures of response (VA, lesion size, and vitreous inflammation) were improved equally in both treatment groups. Our sample size was powered adequately ($\alpha = 0.05$ and $\beta = 0.2$) to determine a difference in retinal lesion size reduction as small as 20%, which seems to be an acceptable limit in clinical terms. However, if a study were required to demonstrate a size reduction difference as small as 2.25%, which was observed in the current study, a sample size of 1860 would be required in each group.

A recent evidence-based literature review concludes there is inadequate evidence to support the routine use of antibiotics in the treatment of acute toxoplasmic retinochoroiditis.³¹ Even though the active lesion may be self-limited, treatment with antibiotic agents and steroids has been well established in clinical practice. Our study was based on the assumption that classic therapy is effective in promoting resolution of toxoplasmic retinochoroiditis; however, it should be stressed that neither treatment regimen was compared with the natural course of the disorder. Considering the long-term consequences of irreversible visual loss and suggestive evidence that treatment can reduce the size of retinal scars, it would seem reasonable to treat active ocular toxoplasmosis when the side effects of treatment are limited.

The results of this study suggest trimethoprim/sulfamethoxazole as an alternative to classic treatment, with greater availability, less cost, and a safer drug profile in immunocompetent patients with two functional eyes and with lesions outside of immediate ($>500 \mu\text{m}$) proximity to the macula. As such, we would not currently recommend using trimethoprim/sulfamethoxazole for active central foveal lesions.

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Discussion

by

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Drs Soheilian et al are to be commended for undertaking the difficult task of studying treatment for ocular toxoplasmosis. It is difficult because toxoplasmosis is a self-limited disease in immunocompetent patients, and there can be substantial variation in the severity and duration of active episodes, based on host, parasite, and possibly environmental factors that remain poorly understood.¹ Also, the duration of treated disease varies with the size of lesions.² Demonstrating that the natural history of the disease has been altered by treatment therefore can be problematic.

Numerous drug regimens have been used for treatment of toxoplasmic retinochoroiditis, but there is no consensus among uveitis specialists as to which regimens are best.³ Furthermore, there are few clinical studies in the medical literature that compare drugs. Thus, additional research is needed to aid clinicians in choosing from among available agents. The authors have chosen appropriate agents for comparison in the current study. Pyrimethamine, sulfadiazine, and oral corticosteroid (classic therapy) is the most commonly used regimen³ and had been considered the standard against which other treatments should be evaluated. The commercially available combination of trimethoprim and sulfamethoxazole is gaining popularity among clinicians as an alternative therapy,³ but there has been little published evidence to support this shift. Trimethoprim/sulfamethoxazole is assumed to be effective on the basis of laboratory studies, treatment of nonocular *Toxoplasma gondii* infections in patients with AIDS, and clinical experience described in small case series. A study in Brazil has

shown that trimethoprim/sulfamethoxazole can reduce the risk of recurrent toxoplasmic retinochoroiditis when administered intermittently on a long-term basis.⁴ Cost and convenience are other, practical advantages. On the other hand, in a review of the medical literature Holland and Lewis³ found laboratory studies demonstrating that the combination of trimethoprim and sulfamethoxazole is less effective than the combination of pyrimethamine and sulfadiazine against *T. gondii*.

In reporting the results of their trial, the authors have provided valuable information, including the fact that the 2 regimens seem to have a comparable effect by some measures. There are several factors, however, that limit readers' ability to interpret the data and apply them clinically. There was a substantial amount of missing data; 17% of patients were lost to follow-up, and investigators were unable to assess the primary outcome measure for an additional 17% of those who completed the study. Also, subjects received lower medication doses than are commonly used in clinical practice. Nearly half of respondents to an American Uveitis Society survey used 50 mg of pyrimethamine daily to treat ocular toxoplasmosis (vs. 25 mg daily in the current study), and the dose cited most commonly by respondents for sulfadiazine was 4 g daily (vs. 2 g daily in the current study).³ The authors do discuss a potential dose effect in contrasting their results to those of Rothova et al,² who found classic therapy to be more effective than trimethoprim/sulfamethoxazole in a comparative but nonrandomized study. They attributed the discrepancy in results possibly to the use of a higher trimethoprim/sulfamethoxazole dose for a longer duration in the current study. It should be noted, however, that they also used a lower dose of both pyrimethamine and sulfadiazine; Rothova et al² used 50 mg of pyrimethamine and 4 g of sulfadiazine daily, twice the dose of each drug used in the current study. Lower doses are undoubtedly associated with reduced toxicity as well, which may explain the low rate of complications in the current study, when compared with previous reports. Finally, the authors treated patients for a standard 6-week course of

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