Short-term Results of Two Treatment Regimens in Ocular Toxoplasmosis: Trimethoprim/Sulfamethoxazole versus Pyrimethamine and Sulfadiazine

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ABSTRACT

Purpose: To compare the efficacy of classic treatment for ocular toxoplasmosis (pyrimethamine, sulfadiazine and predinsolone) with a regimen consisting of trimethoprim/sulfamethoxazole (TMP/SMX) [co-trimoxazole] plus predinsolone.

Methods: In a prospective randomized single-blind clinical trial, 59 patients with active ocular toxoplasmosis were randomly assigned to two treatment groups: 29 were treated with pyrimethamine/sulfadiazine and 30 patients received TMP/SMX. Treatment consisted of six weeks treatment with antibiotics plus steroids. Anti-toxoplasmosis antibodies (IgM and IgG) were measured using ELISA. Outcome measures included changes in retinochoroidal lesion size after six weeks of treatment, visual acuity before and after intervention, adverse drug reactions during follow up and rate of recurrence.

Results: Active toxoplasmosis retinochoroiditis resolved in all patients over six weeks of treatment with no significant difference in mean reduction in retinochoroidal lesion size between the two treatment groups (61% reduction in the classic treatment group and 59% in the TMP/SMX group, P = 0.75). Similarly no significant difference was found in visual acuity after treatment between the two groups [mean visual acuity after treatment was 0.12 LogMAR (20/25) in classic treatment group and 0.09LogMAR (20/25) in TMP/SMX group, P = 0.56]. Adverse events were similar in both groups with one patient in each suffering from any significant drug side effects. The overall recurrence rate after 14 months of follow up was 6.7% with no significant difference between the treatment groups (P = 0.48).

Conclusion: Drug efficacy in terms of reduction in retinal lesion size and improvement in visual acuity was similar between a regimen of TMP/SMX and the classic treatment of ocular toxoplasmosis with pyrimethamine and sulfadiazine. Therapy with TMP/SMX appears to be an acceptable alternative for the treatment of ocular toxoplasmosis.

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Introduction

Ocular toxoplasmosis is caused by the intracellular parasite, toxoplasma gondii and is a major source of preventable blindness particularly in young people. It accounts for 15-17% of all cases of uveitis and 25% of posterior uveitis in the United States and more than 85% of posterior uveitis in...
In a previous study conducted at our institution, toxoplasmosis was identified as the most common cause of posterior uveitis, accounting for 54.5 percent of cases. The prevalence of infection with toxoplasmosis gondii increases with age and varies depending on geographic region. This disease usually manifests as a late reactivation of a congenital infection, although recent studies suggest an acquired etiology with two-thirds of all cases of ocular toxoplasmosis potentially acquired after birth.

The goal of medical treatment is to arrest the multiplication of the parasite during the period of active retinochoroiditis in order to prevent irreversible damage to the retina and optic nerve, which would lead to permanent visual loss. Currently the most common treatment consists of pyrimethamine and sulfadiazine plus corticosteroids aimed at controlling the reactivation of parasites from dormant cysts and the associated inflammatory reaction, especially when the lesion is located within or near the macula. 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 co-administration of folic acid for guarding against leukopenia and thrombocytopenia. In addition, these drugs are not readily available in some areas 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, TMP/SMX, spiramycin, minocycline, azithromycin, atovaquone, and intravitreal injection of clindamycin and dexamethasone. Further study into a safer and simpler treatment for toxoplasmosis is warranted given that most current treatments are not free of significant toxicity.

Treatment of ocular toxoplasmosis with TMP/SMX is currently a treatment option, but no randomized controlled study has specifically compared this regimen with the classic therapy. TMP/SMX therapy works like the combination of pyrimethamine and sulfadiazine, whose action is mediated through inhibition of the 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 TMP/SMX. The use of TMP/SMX has gained popularity among uveitis specialists, such that the use of this drug regimen from 1991 to 2002 rose from 5% to 28%. TMP/SMX has been used for prophylaxis of toxoplasmosis encephalitis in patients with AIDS, which may explain why it has similarly become a favorable option with ophthalmologists. More recently TMP/SMX prophylaxis has shown efficacy in preventing recurrence of ocular toxoplasmosis. The most common side effects of TMP/SMX are usually mild gastrointestinal symptoms (nausea, vomiting, abdominal pain, and infrequently diarrhea) and mild skin rashes. Severe dermatological reaction (e.g. Stevens-Johnson syndrome) occurs rarely. As such the long-term use of this drug regimen is usually well-tolerated. Furthermore, while TMP/SMX works in a similar mechanism as the classic agents, it is known to be less toxic to hematopoiesis and eliminates the need for folic acid supplementation as well as hematologic evaluation except in patients with renal failure or advanced age. It is a relatively inexpensive and readily available drug that is also available in a liquid formula for pediatric patients.

In this study, we compare the efficacy and safety of TMP/SMX with that of classic therapy in ocular toxoplasmosis.

**Methods**

This clinical trial was conducted in a controlled, randomized single blind fashion. Patients were clinically diagnosed 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 with or without the accompaniment of an old lesion. The following were used as inclusion criteria for our study: 1) location of lesion within zone 1 of the retina (region extending
3,000 microns from the foveal center)\textsuperscript{12} or a lesion greater than 2 disc diameters in size with 3-4\textsuperscript{+} vitreous inflammation within zones 2 or 3. (Zone 2 was defined as the region extending anteriorly from the border of zone 1 to the equator, and zone 3 as the region from the border of zone 2 to the ora serrata).\textsuperscript{12} 2) Presence of retinal lesion at least 500 microns away from 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 less than 20/200 in the fellow eye. 2) Location of the lesion within the center (500 microns) of the macula. 3) Development of allergic reaction to the medication. 4) Leukopenia (WBC <5,000) or platelet count less than 120,000/ml. 5) Lesions smaller than 2 disc diameters in zones 2 and 3.

Patients were recruited from the Labbafinejad Medical Center Uveitis Clinic in Tehran, Iran from January 2000 to the end of February 2002. Patients consented to participation in the study and the study was approved by the ethics committees of the hospital and the Shaheed Beheshti Medical University. Of the seventy-one patients enrolled in the study, fifty-nine patients (36 men and 23 women) are included in this report. Twenty-nine patients were treated with the classic regimen consisting of pyrimethamine and sulfadiazine, and 30 patients were treated with TMP/SMX. Classic treatment consisted of an initial dose of pyrimethamine 100 mg daily for two days followed by 25 mg dose daily, sulfadiazine 2 g daily for two days followed by 500 mg every six hours and folinic acid 5 mg daily. In the second group, treatment consisted of two tablets of TMP/SMX (TMP 80 mg, and SMX 400 mg) every 12 hours. In both groups, treatment was continued for six weeks and oral prednisolone was administered 1 mg/kg daily starting from the third day of therapy and the dose was tapered over two weeks.

Response to treatment was identified as sharpening of the lesion border with or without hyperpigmentation and resolution of vitreous inflammation.\textsuperscript{1,4,24,25} Recurrence was defined as the appearance of an active lesion adjacent to an old scar or elsewhere.\textsuperscript{4} Patients were examined by an ophthalmologist on day 1, end of weeks 1 through 6, and every 3 months. All patients underwent measurement of visual acuity and anterior vitreous inflammation according to the system devised by Kanski and Kimura\textsuperscript{27}, and Thygeson and Hogan\textsuperscript{28}. 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 greatest length diameter (GLD) of the lesion. Two masked retina specialists evaluated the fundus photographs independently on day 1 and week 6 of therapy. Serum measurements of IgG and IgM anti-toxoplasmosis antibodies (ELISA) were obtained once in all cases; weekly complete blood cell and platelets counts were performed in patients on classic treatment regimen. Patients were followed after completion of treatment for at least 14 months. Lesion size reduction was considered as the primary outcome measure and visual acuity, vitreous inflammation, adverse drug reaction and recurrence rate were secondary outcome measures. Independent sample \textit{t}-test was performed to compare age, lesion size reduction, and visual acuity before and after treatment between groups. Chi-square test was employed to compare sex distribution, vitreous inflammation before and also after treatment and recurrence rate between groups. Paired \textit{t}-test was also used to compare visual acuity and lesion size before and after treatment. McNemar test was performed to compare vitreous inflammation before and after treatment in each group. P values less than 0.05 were considered significant.

\textbf{Results}

Of seventy-one patients initially recruited, 35 patients were randomly assigned to receive classic therapy and 36 patients to treatment with TMP/SMX. Six patients in the TMP/SMX group (one due to development of drug allergy and five due to incomplete follow up) and six patients in the classic
treatment group (one due to development of allergic reaction to sulfadiazine and five others 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 TMP/SMX group consisted of 18 men (60%) and 12 women (40%) [P=0.54]. Mean age in the classic therapy group and the TMP/SMX group was 23.5±7.4 (range 12-45) and 26.6±11.7 (range 12-59) [P=0.23]. There was no significant difference between the two groups with regard to age, gender and visual acuity before treatment [Table 1]. Duration of follow-up was similar in both treatment groups with a mean of 14.9±3.8 (range 9-21) months in the classic group and 13.3±4.5 (range 5-22) months in the TMP/SMX treatment group.

**Table 1:** General characteristics of patients before and after treatment (N=59)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Classic treatment group =29</th>
<th>Co-trimoxazole group =30</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18 (62.1%)</td>
<td>18 (%60)</td>
<td>0.54</td>
</tr>
<tr>
<td>Female</td>
<td>11 (%37.9)</td>
<td>12 (%40)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.5 ±7.4 (12-45)</td>
<td>26.6±11.7 (12-59)</td>
<td>0.23</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>14.9±3.8</td>
<td>13.3 ± 4.5</td>
<td>0.17</td>
</tr>
<tr>
<td>Presence of previous retinal scar</td>
<td>15 (%51.7)</td>
<td>14 (%46.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Visual acuity before treatment</td>
<td>0.68 LogMAR (20/100)</td>
<td>0.57 LogMAR (20/80)</td>
<td>0.69</td>
</tr>
<tr>
<td>Visual acuity after treatment</td>
<td>0.12 (20/25)</td>
<td>0.09 (20/25)</td>
<td>0.56</td>
</tr>
<tr>
<td>Improvement in visual acuity</td>
<td>0.56 LogMAR (5.5 Snellen lines)</td>
<td>0.52 LogMAR (5 Snellen lines)</td>
<td>0.75</td>
</tr>
<tr>
<td>Disappearance of vitreous cells in 6 weeks (0-trace cell)</td>
<td>20(%69)</td>
<td>17(%56.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Positive IgG titer</td>
<td>29 (%100)</td>
<td>30 (%100)</td>
<td>1</td>
</tr>
<tr>
<td>Positive IgM titer</td>
<td>13 (%44.8)</td>
<td>9 (%30)</td>
<td>0.18</td>
</tr>
<tr>
<td>Recurrence 14 months after treatment</td>
<td>2 (%6.9)</td>
<td>2 (%6.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>1 (%2.9)</td>
<td>1 (%2.8)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Both treatment groups responded similarly to treatment with improved visual acuity. Mean visual acuity before treatment was 0.68 LogMAR (20/100, range: 20/20-CF at 40cm) and 0.57 LogMAR (20/80, range: 20/20-CF at 40cm) in the classic therapy group and in the TMP/SMX group respectively (P= 0.52) [Table 1]. Mean visual acuity achieved after treatment was 0.12 Log MAR [20/25 (20/20-20/160)] in the classic therapy group and 0.09 LogMAR [20/25 (20/20-20/160)] in the TMP/SMX group (P= 0.56). Within each group, there was significant improvement in visual acuity after treatment; VA increased by 0.56 LogMAR units (5.5 lines) in the classic therapy group [P value<0.01] and by 0.52 LogMAR units (5 lines) in the TMP/SMX group [P value<0.01]; however, there was no statistically significant difference in visual improvement between the two treatment groups (P= 0.75). (Graph 1)
Of the 59 patients in the study, we were able to measure retinal lesion size in forty-nine. Five patients in the classic therapy group (one individual due to media opacity, and 4 due to failure to obtain a second fundus photograph) and five patients in the TMP/SMX group (two individuals due to media opacity, one due to lack of initial fundus photography and two others due to unavailability of a second fundus photograph) were excluded from this outcome measure. There was no significant difference between the two treatment groups in terms of reduction in retinal lesion size; patients in the classic therapy group had a mean of 61 percent (range 10-100%) reduction and patients in the TMP/SMX group demonstrated a mean of 59 percent (10-100%) reduction in lesion size after six weeks of treatment (P = 0.75).

Reduction of vitreous inflammation was also not different in the groups with 20 patients (69%) in the classic therapy group and 17 patients (56.7%) in the TMP/SMX group showing trace to no inflammatory cells after treatment (P = 0.24). In twenty-nine patients (49.2%), a previous retinal scar was detected; of these 15 patients (51.7%) were assigned to classic therapy and 14 patients (46.7%) were in the TMP/SMX group (P = 0.44). Anti-toxoplasmosis antibody analysis revealed positive IgG titers in all patients in both treatment groups. IgM titers were positive in 13 (44.8%) and 9 (30%) cases in the classic and the TMP/SMX groups respectively (P = 0.18).

During the follow up period, a total of 4 recurrences occurred in the patient population, of which two cases (6.9%) were observed in the classic therapy group and two cases (6.7%) in the TMP/SMX group (P = 0.48). In the classic treatment group one patient had three recurrence episodes and the other patient had two episodes of recurrence. In the TMP/SMX group, one patient experienced two recurrence episodes, and the other case had a single recurrence episode.
Adverse drug reactions were limited to one patient (2.9%) in the classic therapy group and one patient (2.8%) receiving the TMP/SMX regimen; in both cases the drug reaction was development of a rash. Both patients were taken off their respective medication regimen and excluded from the study.

Discussion

Our study revealed no significant difference between classic treatment with pyrimethamine and sulfadiazine and TMP/SMX for ocular toxoplasmosis retinochoroiditis in terms of reduction in lesion size. Mean reduction in size of retinal lesion was 61% in the classic therapy group and 59% in the TMP/SMX group. In a similar prospective multi-center study by Rothova and associates, significant reduction in retinal lesion (defined as at least one-half disc diameter reduction in the diameter of lesion) was found in 49% of patients receiving classic therapy and 11% of patients receiving TMP/SMX. 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.

However, we evaluated response to treatment by the percentage of decrease in the size of the initial lesion. Moreover, Rothova et al. used a four-week period of treatment whereas our patients were treated for 6 weeks. There is also a difference in the treatment regimen between the two studies, with Rothova et al. utilizing a 960mg dose of TMP/SMX twice daily during first two weeks and then 380 mg two times per day for the last two weeks, whereas in our study we continued the initial 960mg dose for the entire 6 weeks of treatment. As such, it is likely that the higher dose and longer duration of TMP/SMX treatment in our study caused the greater response.

Response to treatment measured by change in visual acuity revealed a non-significant difference between the treatment groups with a 0.56 Log MAR (5.5 lines of vision) improvement in acuity in the classic therapy group and 0.52 Log MAR (5 lines of vision) improvement in patients receiving TMP/SMX. In a study by Opremcak, mean visual acuity after treatment in patients receiving TMP/SMX was 20/30 with an improvement of 4.6 lines, which is consistent with our findings.

Similarly, in Rothova’s study, which utilized three different treatment regimens, including classic and TMP/SMX, there was no significant difference in improvement in visual acuity between the study groups after treatment. In a retrospective study of 154 patients with active uveitis, Bosch-Driessen et al also found no significant difference in visual acuity between patients receiving different treatment regimens at the conclusion of therapy. Nevertheless, measuring the effect of treatment on visual acuity 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 six weeks of therapy, there was resolution of signs of vitreous inflammation in 69% of patients receiving classic therapy and 56.7% of patients on TMP/SMX. Bosch-Driossen et al reported resolution of vitreous inflammation in 71% of their patients after four 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. 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.

There were 4 cases of recurrence (6.7%) in our entire patient population with an average follow up of 14 months with no significant difference between treatment groups. In the Rothova study the
rate of recurrence after one year was 2.7%, with mean recurrence rate of 41% after two years follow up and no particular treatment regimen was found to be superior in preventing recurrences.

Opremcak\textsuperscript{11} found only one case of recurrence (6.25\%) in his patient population after ten months follow up, while in another study Bosch-Driessen and Rothova reported a 29\% rate of recurrence within one year after treatment.\textsuperscript{29} An even higher rate of recurrence (56\%) within one year was reported by Bosch-Driessen and Verbraak\textsuperscript{14} in a population of patients receiving classic therapy with pyrimethamine and sulfadiazine. As evident, the rate of recurrence is greatly variable as reported by different researchers and is positively correlated with the period of follow up.\textsuperscript{30} Other factors, which 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 was limited to one case (3.4\%) in the classic therapy group and one patient (3.3\%) receiving TMP/SMX. Similar to other published studies these adverse reactions resolved with withdrawal of treatment.\textsuperscript{2,11} In Rothova’s study the rate of adverse drug reactions in patients receiving TMP/SMX was only 4\%, while 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.\textsuperscript{14} The different rates of adverse drug reactions may have been due to the minimal therapeutic dose (25mg daily pyrimethamine and 2g daily sulfadiazine) utilized in patients receiving classic therapy in our series. Studies with greater sample size are required to demonstrate the true incidence of such events.

The decision to pursue TMP/SMX as an alternative drug regimen to classic treatment with pyrimethamine and sulfadiazine in this study was multi-faceted. First, since the appearance of Opremcak and associates’ 1991 study,\textsuperscript{11} comparing the efficacy of two different TMP/SMX regimens for ocular toxoplasmosis, there appears to be increasing acceptance of this drug regimen by uveitis specialists; its use rising from 5\% in 1991 to 28\% in 2002.\textsuperscript{12} Moreover, from a theoretical perspective TMP/SMX is a logical treatment choice because this combination drug acts in a similar fashion to pyrimethamine and sulfadiazine in inhibiting synthesis of tetrahydrofolic acid and its efficacy against toxoplasma gondii has been established in vitro.\textsuperscript{20}

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 TMP/SMX, competing alternative treatments to classic therapy include clindamycin, macrolides (azithromycin and spiramycin), allopurinol, and atovaquone.\textsuperscript{12} Clindamycin, while being effective in the treatment of ocular toxoplasmosis, is an antibiotic highly associated with the development of pseudomembranous colitis from C. difficile, manifesting as limited diarrhea to fatal toxic megacolon.\textsuperscript{31,32} 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.\textsuperscript{14}

A smaller study demonstrating azithromycin’s efficacy failed to compare it with classic therapy.\textsuperscript{33} However, another study which compared spiramycin to classic treatment, found monotherapy with spiramycin to be superior in terms of reduction of active disease duration and side effects.\textsuperscript{34} A recent unpublished study has offered hope in the use of allopurinol as an anti-inflammatory treatment, yet this study did not compare allopurinol with the classic regimen.\textsuperscript{35}

Another agent, atovaquone (hydroxynaphthoquinone) has been used effectively in treatment of active disease and has been shown to be relatively safe in terms of side effects,\textsuperscript{36} but this regimen too was not compared with classic treatment and its use appears to be limited by cost as well as lack of clinical experience.

The results of this study demonstrated TMP/SMX to be as effective as classic treatment for toxoplasmosis retinochoroiditis; this finding is substantiated by similar clinical studies with TMP/SMX.\textsuperscript{11} Although one study found a smaller reduction in lesion size in patients on TMP/SMX.
when compared to classic treatment and no treatment, there was a trend toward shorter duration of inflammatory activity with TMP/SMX. Our findings are strengthened by the randomized and controlled nature of this study and the relatively large number of patients in each treatment group.

Potential weaknesses include our inability to completely mask evaluating physicians to the patients' assigned treatment regimen and the inability to obtain fundus photographs in some patients. Nevertheless, the positive response to treatment is not likely to have been significantly altered as all three measures of response (visual acuity, lesion size, and vitreous inflammation) were equally improved in both treatment groups.

A recent evidence-based literature review concludes that there is inadequate evidence to support the routine use of antibiotics in the treatment of acute toxoplasmic retinochoroiditis. Even though the active lesion may be self-limited, treatment with antibiotic agents and steroids has been well established in clinical practice. 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 TMP/SMX as an alternative to classic treatment with greater availability, less cost and safer drug profile in immune-competent patients with two functional eyes and with lesions outside immediate proximity (> 500 microns) to the macula. As such, we would not currently recommend using TMP/SMX for active central foveal lesions.

References: