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ABSTRACT

Purpose: To evaluate the efficacy and safety of trimethoprim/sulfamethoxazole and azithromycin combination for the treatment of ocular toxoplasmosis. *Methods*: Nineteen ocular toxoplasmosis patients treated with trimethoprim/sulfamethoxazole and azithromycin ± corticosteroid combination were retrospectively reviewed. Demographic data, clinical findings, the time interval until resolution of inflammation, recurrences, and drug side effects were collected. *Results*: The mean follow-up time of the patients was 25.0 ± 22.5 (range; 6 –66) months. Final visual acuity improved with a mean of 6 ± 4 lines in 15 patients (78.9%). Inflammatory findings began to subside within 14.8 ± 10.0 days. Three patients (15.8%) had recurrent attack. Only 1 patient (5.3%) had side effects from therapy. *Conclusions*: Trimethoprim/sulfamethoxazole and azithromycin combination is an effective and safe treatment modality for the treatment of ocular toxoplasmosis.

Keywords: azithromycin; ocular toxoplasmosis; recurrence; trimethoprim/sulfamethoxazole; visual acuity

Ocular toxoplasmosis is the most common cause of posterior uveitis leading to preventable blindness, particularly in young people.[1] It is characterized with recurrent episodes of retinochoroiditis both due to direct tissue destruction of live organisms or the inflammatory reaction itself.[2] The aim of treatment for ocular toxoplasmosis is to stop the multiplication of parasites that leads to retinal damage and to lessen the inflammatory process that may aggravate the retinal damage.[3] Although antiparasitic treatments have therapeutic effect at the active stage of retinochoroiditis, recurrences cannot be prevented since they have no effect on dormant tissue cysts.[4] The combination of pyrimethamine and sulfadiazine is a well-known and widely used treatment regimen for ocular toxoplasmosis. This combination therapy, however, has important side effects, leading the clinician to prescribe folinic acid and to perform serial complete blood cell counts.[1,5,6] Additionally; it is not easily available in some countries like Turkey. Studies dealing with different medications are being performed to find a more tolerable, effective, and inexpensive treatment modalities.[4–7]

Trimethoprim/sulfamethoxazole acts like pyrimethamine and sulfadiazine via inhibiting DNA synthesis without the need for folinic acid supplementation. It is found to be effective in preventing the recurrence of ocular toxoplasmosis.[8] Azithromycin has been shown to be effective on both tachyzoites and tissue dormant cysts in vivo and in vitro.[6] Its availability, low-toxicity profile and ability to cross the blood–retinal barrier turns azithromycin into a treatment of choice in ocular toxoplasmosis.[4]

In this study, we investigated the efficacy and safety of azithromycin and trimethoprim/sulfamethoxazole combination for ocular toxoplasmosis treatment and evaluated its effect on recurrence rates and visual outcome.

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MATERIALS AND METHODS

The records of 19 ocular toxoplasmosis patients treated with trimethoprim/sulfamethoxazole and azithromycin ± corticosteroid combination and who had a follow-up period of 6 months at least, were retrospectively reviewed from the records of a tertiary referral hospital's Uvea and Behcet disease department. Demographic data, laboratory findings, detailed baseline and follow-up ophthalmic examinations, including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, and dilated fundus examination, were noted. The diagnosis of ocular toxoplasmosis was based on clinical findings and supported with the presence of toxoplasma-specific immunoglobulin M (IgM) or IgG antibodies. The treatment was started if the retinal lesion was located at the posterior pole or close to vascular arcades. All patients were treated with the same antiparasitic combination protocol: azithromycin 1000 mg on the first day and then 500 mg per day for 8–4 days and trimethoprim/sulfamethoxazole (800/160 mg) two times daily for 6–8 weeks according to clinical response. The complementary steroid therapy was added in case of severe vitritis and/or lesion located at posterior pole leading to visual acuity decrease. Patients were examined weekly up to 4 weeks and then with the frequency determined by clinical evaluation. All follow-up visits were performed by one clinician (PO) to avoid variability in clinical assessment. The criterion for good response to treatment was subsiding of inflammation (the sharpening of the lesion borders, flattening of the lesion surface, and lessening of the vitritis). Recurrence was defined as the presence of a new active retinal lesion. Potential medication discomforts and toxicities were noted.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

RESULTS

From the 19 patients recruited to the study 12 (63.2%) were female and 7 (36.8%) were male. The mean age at presentation was 30.68 ± 14.39 (range; 12–64) years. The mean follow-up time of the patients was 25.0 ± 22.5 (range; 6–66) months. Eight patients (42.1%) were having their first attack, while the rest (57.9%) were recurrent cases. Additional use of steroid was needed in 16 patients (84.2%). Only 1 patient (5.3%) who presented with active lesion at macula had experienced visual acuity decline of 5 lines in Snellen chart, although the lesion became inactive in a 1-month period. Three patients (15.7%) had the same visual acuity compared to pretreatment levels. Fifteen patients (78.9%) had better final visual acuities with a mean increase of 6 ± 4 lines when compared to presenting visual acuities. The improvement in visual acuities was statistically significant (paired sample t test, $p < .01$). The mean period between the initiation of treatment and subsiding of inflammatory signs was 14.8 ± 10.0 days. Recurrence was observed in 3 patients (15.8%) within a mean interval of 24.0 ± 18.2 (3, 33, and 36) months. The combination therapy was very well tolerated in all but one patient who had diarrhea due to trimethoprim/sulfamethoxazole.

DISCUSSION

Ocular toxoplasmosis is a recurrent necrotizing retinochoroiditis and is one of the most common causes of posterior uveitis both in tertiary referral and community-based practices.[9,10] Although the disease is self-limiting, current practices are more likely to treat ocular toxoplasmosis compared to past.[11] However, some controlled studies expressed that the current treatment modalities are only of limited benefits.[5,12] Although a literature review stated an inadequate evidence to support the routine use of antiparasitic medication,[13] the survey conducted by the American Uveitis Study group found a greater tendency among uveitis specialists to treat patients, with 15% treating all cases with no exclusion.[10] Alternative treatment choices are being investigated nowadays. Among them, trimethoprim/sulfamethoxazole and azithromycin are the ones gaining popularity.

In this study evaluating the efficacy of trimethoprim/sulfamethoxazole and azithromycin combination and comparing with the results of the literature, visual acuities improved significantly after the treatment. In 94.7% of all patients final visual acuities were equal or better than the pretreatment levels. Mean improvement of 6 lines was observed compared to pretreatment levels. These results were consistent with the results of Soheilian et al.[9] in which they found no significant difference between trimethoprim/sulfamethoxazole and classic pyrimethamine sulfadiazine treatment. In their study all patients had reached an equal or better final visual acuity in each group. Opremcak et al.[6] also achieved a 4.6-line increase after the treatment. Studies comparing different treatment regimens have failed to find significant differences in terms of final visual acuity.[8,14] We believe that visual acuity is not a good parameter for assessment of the therapeutic success since the lesion localization and proximity to macula have great influence on the outcome.

The mean interval for inflammatory findings to subside was 14.8 ± 10.0 days in our study. Soheilian et al.[10] have found that at the end of the 6 weeks of treatment, the

resolution in signs of inflammation was seen in 56.7% of trimethoprim/sulfamethoxazole and 69% of classic regimen patients. Bosch-Driessen et al.[14] reported resolution in 71% of patient at the end of a 4-week treatment period with the classic therapy. In our study, the inflammation disappeared before the 4th week of the treatment in 14 patients (73.7%). Rothova et al.[4] have studied azithromycin and have concluded that in 63.6% of patients inflammatory activity disappeared at the end of 4 weeks of treatment. The combination therapy that we used in this study seems to accelerate the resolution of inflammation when compared to some studies in the literature.[4,10,14] Both the appearance of inflammation resolution and complete resolution seemed to be faster.

One of the main concerns about treating ocular toxoplasmosis is to prevent recurrences. When evaluating the recurrence rates of previous studies, it is important to consider the length of the follow-up. The recurrence rates in literature should be evaluated with the length of the follow-up period. The recurrence rate in our study was 15.8% with 3-, 33-, and 36-month intervals from the first attack. For the 11 patients who were followed beyond 12 months, the recurrence rate was 9.0% at 12 months. This rate was reported to be 27.3% for azithromycin in a 12-month follow-up period by Rothova et al.[4] Soheilian et al.[10] have demonstrated that the recurrence was 10.3% in both pyrimethamine sulfadiazine and trimethoprim/sulfamethoxazole groups within 24 month follow-up. Bosch-Driessen et al.[15] have found 56% of recurrence rate in a 12-month follow-up. As seen obviously, the recurrence rate varies in different studies with different regimens.

A variety of studies have shown that the discontinuation of traditional therapies due to the side effects was up to 40% in immunocompromised and 26% in immunocompetent patients.[5,16] In our study trimethoprim/sulfamethoxazole was discontinued only in 1 patient (5.3%) due to diarrhea. Rothova et al.[4] has not faced any side effects with azithromycin. Trimethoprim/sulfamethoxazole toxicity, presented as cutaneous erythema that had resolved with discontinuation of the medication, was seen in 6.6% in the study of Silveira et al.[8]

As a conclusion, the combination of trimethoprim/sulfamethoxazole and azithromycin may be a good and safe alternative in ocular toxoplasmosis treatment since it improves visual acuity, hastens the resolution of inflammation, and decreases recurrence rates. However, the validity of this combination therapy might be best understood with large-scale, prospective randomized studies comparing different medications.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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