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Crescent Journal of Medical and Biological Sciences
Vol. 4, No. 2, April 2017, 80–84
eISSN 2148-9696

Comparison of Azithromycin and Pyrimethamine/Sulfadiazine Treatment in Ocular Toxoplasmosis in North West of Iran

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Abstract

Objective: Ocular toxoplasmosis (OT), characterized by necrotizing retinochoroiditis, scar formation and decreased vision, is recognized as the most prevalent cause of posterior uveitis in Iran. Although pyrimethamine/sulfadiazine combination remains the standard treatment particularly for patients with sight-threatening lesions, intolerance, inaccessibility and adverse drug reactions to this regimen have imposed us to seek for alternative treatments.

Materials and Methods: In this prospective randomized control clinical trial study, 72 patients with active, non-vision threatening toxoplasmic chorioretinitis were randomly divided into 2 treatment regimen: 36 patients treated with standard protocol with pyrimethamine/sulfadiazine, and 36 patients received azithromycin for 6 weeks. All patients were followed up for 24 months. The clinical outcomes measured before and after intervention were, time to disease inactivity (lesion borders sharpening and scarring), changes in the size of retinochoroidal lesion, rate of recurrence, adverse drug reactions and visual acuity (VA).

Results: No significant difference was noted between the 2 groups regarding age, gender, and VA before treatment. Significant improvement was noted in VA for each group during treatment. VA increased by 0.39 logMAR units in group 1 ($P=0.00$) and 0.35 logMAR units in group 2 ($P=0.00$). There was no statistically significant difference between the 2 groups concerning visual improvement ($P=0.33$) and reduction in retinal lesion size and activity. There were totally 22 cases who experienced recurrences during the follow up period (4 [11.1%] patients of control group and 18 [50%] of intervention group [$P=0.00$]), indicating significant lower recurrence in control group. Treatment tolerance was significantly better for the azithromycin group due to lower adverse drug reactions ($P=0.00$).

Conclusion: Azithromycin at a dose of 250 mg/d was shown to be effective for the treatment of active, non-vision threatening toxoplasmic retinochoroiditis similar to classic treatment with Pyrimethamine/Sulfadiazine regimen. However, recurrences and adverse drug reactions seem to differ significantly which notes the need for further studies and also vigilant selection of treatment protocols.

Keywords: Azithromycin, Toxoplasmosis, Uveitis, Chorioretinitis.

Introduction

An obligate intracellular protozoan, *Toxoplasma gondii* is a leading cause of preventable visual loss by ocular toxoplasmosis particularly in young people (1). It infects almost 33% of the world's population (2). In the United States 15% to 17% of all cases with uveitis and 25% of posterior uveitis were reported to be caused by *T. gondii*, and in Brazil it accounts for >85% of posterior uveitis (3). It was recognized as a prevalent cause of posterior uveitis in a tertiary center in Iran, accounting for 54.5% of all cases (4). This infection was characterized by necrotizing retinochoroiditis, scar formation and decreased vision in the eye.

More recent reports concerning epidemiology of ocular toxoplasmosis (OT) confirmed that acquired *T. gondii* infection occurs in all age groups, including children, and manifestations of ocular disease can rise after infection without noticeable concurrent systemic signs or symptoms(5). This finding highlights the importance of primary prevention strategies, targeting not only pregnant women, but also children and adults at risk.

Previously, only 1% to 3% of patients with acquired infection were believed to develop OT. However, serologic studies suggest that OT is associated with acquired infection, more than what was believed previously.

There is no absolute treatment approach for the disease and the efficacy of current treatments seems to be controversial (6-8). Some researchers have studied the efficacy of antibiotics in active OT but efforts in this field have not led to a consensus on selection of antibiotics.

Received 9 August 2016, **Accepted** 4 February 2017, **Available online** 9 February 2017

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Currently, the suggested treatments for OT act against the tachyzoite form of protozoan; therefore, the elimination of the encysted form (bradyzoite) is not accomplished.

The classic treatment of OT usually consists of triple therapy: Pyrimethamine (loading dose: 50-100 mg; treatment dose: 25-50 mg/d), which is the most effective agent contained in most drug regimens, sulfadiazine (loading dose: 2-4 g; treatment dose 1.0 g 4 times daily), and prednisone (treatment dose: 0.5-1.0 mg/kg/d, depending on the severity of the inflammation). Since sulfonamides and pyrimethamine inhibit folic acid metabolism, folinic acid (leucovorin 5 mg every other day) should be administered to prevent bone marrow suppression (9). This standard treatment is expensive, might have major adverse side effects (such as skin rash, kidney stones and Stevens-Johnson syndrome) and could not be readily available in some areas (10). On other hand patient compliance is low in that patient needs to take up to 10 pills daily and blood cell count and platelet monitoring are required weekly for pyrimethamine administration (1). Although sulfadiazine/pyrimethamine combination remains the standard treatment particularly for patients with sight-threatening lesions, intolerance, inaccessibility and adverse drug reactions to this regimen have prompted researchers for alternatives with better events (11).

Azithromycin is a treatment option for OT. Azithromycin alone has been shown to be effective against *T. gondii* in laboratory studies, and is believed to be an effective treatment for patients with active toxoplasmic retinochoroiditis (11). Furthermore, it is relatively inexpensive, has a low rate of side effects with better compliance, and the patient needs to take up one pill per day.

Although valuable studies have been introduced for OT highlighting the treatment protocols and their efficacy, but no clinical study has specifically compared azithromycin regimen with a standard treatment in Iran. It seems necessary to study the efficacy of present treatments and potential side effects regarding the geographical differences.

This prospective randomized clinical study was conducted to compare the efficacy of azithromycin with the standard treatment (pyrimethamine/sulfadiazine) in non-vision threatening OT and was aimed to evaluate treatment outcomes, disease relapse and adverse drug effects in Nikookari hospital, Tabriz, Iran.

Materials and Methods

This randomized, controlled clinical study was conducted as a single blind clinical trial from January 2014 to October 2016 in an outpatient uveitis clinic in Nikookari eye hospital, Tabriz, Iran. Diagnosis of OT was made for patients clinically by the findings of visual disturbances and whitish yellow appearing areas on retina with a blurred margin matching focal chorioretinal necrotizing lesion with or without accompanying old lesion (11).

Inclusion criteria were: location of the lesion within region extending 3000 μm from the foveal center and at least 500 μm outside the center of the macula, or a lesion with 2 disc diameters or larger in size with 3-4 plus vitritis within the region extending anteriorly from 3000 μm from the fovea to the equator and positive serological evaluation for immunoglobulin G (IgG) and negative for IgM anti-toxoplasmosis antibody.

Exclusion criteria were: Low vision in the fellow eye (visual acuity [VA] of less than 20/200), central lesions (within the 500 μm of the fovea), active intraocular inflammation, patients younger than 18, pregnancy, immunodeficiency, leukopenia (white blood cell count less than 5000) or platelet count less than 120 000/mL, peripheral lesion less than 2 disc diameters or causing ≤2 vitreous inflammation, severe media opacity precluding clear photography, history of intolerance or hypersensitivity to macrolides or pyrimethamine/sulfadiazine, febrile illness or other infectious diseases or history of any antibiotic therapy at last 30 days and any immunodeficiency conditions.

Patients were employed from the Nikookari Hospital Uveitis Clinic, Tabriz, Iran from January 2014 through October 2016.

Seventy-two patients with non-vision threatening OT who met inclusion criteria entered the study. They were assigned to control or intervention arms of the study in a 1:1 ratio, utilizing a computer-generated randomization list. Treatments in both groups started immediately after randomization on the day of presentation. Thirty-six patients were treated with the standard protocol (pyrimethamine/sulfadiazine), and 36 were treated with azithromycin.

An initial loading dose of 100 mg, followed by a dose of 50-mg daily for pyrimethamine, and a loading dose of 2 g followed by 500-mg every 6 hours daily for sulfadiazine, and 5 mg of folinic acid once daily as the classic treatment protocol was used. In the other group, 1 tablet of azithromycin 250 mg daily was used. In both groups, drugs were administered for 6 weeks and oral prednisolone was prescribed with a dosage of 1 mg/kg daily starting 72 hours after initial therapy. Corticosteroid was tapered over 14 days.

All patients were followed for 24 months during which they examined by an ophthalmologist on the first day of treatment and then every 2 weeks until disease inactivity. Further visits set every 3 months from the beginning of treatment for all participants. Complete ocular evaluation, including VA measurement, Vitritis grading (by Kanski (12) and Kimura et al (13) designed system), fundus examination with the slit lamp and indirect ophthalmoscopy and fundus photography were performed at baseline and follow up visits. Serologic testing by enzyme-linked immunosorbent assay (ELISA) confirmed the presence of anti-*T. gondii* IgG antibodies in all patients before enrollment in the clinical trial and complete blood cell and platelet counts were performed weekly in patients with classic treatment regimen. Lesion size was measured by fundus photography, and the reduction in the greatest diameter of the lesion was estimated.

Reduction in the size of lesion was our primary outcome

measure. Recurrence rate (defined as the active focal necrotizing chorioretinal lesion adjacent to an old scar or elsewhere (1)), adverse drug reactions and VA were secondary outcome measures.

Data were analyzed using SPSS software for Windows (SPSS Inc., Chicago, IL, USA). In the statistical analysis independent-sample *t* test, chi-square test and paired *t* test were used. *P* values of less than 0.05 were considered significant.

Results

Seventy-two patients with non-vision threatening active OT who met inclusion criteria entered the study. They were assigned as control (group 1) or intervention (group 2) arms of the study in a 1:1 ratio. 36 patients received pyrimethamine and Sulfadiazine regimen (group 1) and 36 patients received azithromycin regimen (group 2). The initial epidemiological and clinical characteristics of cases in each group are presented in Table 1.

All patients completed the 24 months of study period and final analysis performed for them. Group 1 consisted of 20 males (55.6%) and 16 females (44.4%) and group 2 consisted of 18 males (50%) and 18 females (50%) ($P=0.503$). Mean age in the group 1 and 2 were 37.56 (range, 20-60) and 41.94 (range 20-56) respectively ($P=2.85$). Mean VA before treatment was 0.73 LogMAR (logarithm of the minimum angle of resolution) (20/107 of Snellen acuity) ranging from 20/30 to counting fingers [CF] at 40 cm) in group one and 0.82 LogMAR (20/132 of Snellen acuity) ranging from 20/30 to CF at 40 cm in group 2 ($P=0.49$). Antitoxoplasmosis antibody titer analysis demonstrated positive IgG and negative IgM titers in all patients in both groups. There was no statistically significant difference between 2 groups considering age, gender, initial VA and antitoxoplasmosis antibody titers before treatment (Table 1).

Mean VA after treatment was 0.33 LogMAR (20/42 of Snellen acuity, ranging from 20/20 to 20/200) and 0.46 LogMAR (20/57 of Snellen acuity, ranging from range 20/20 to 20/399) for group 1 and 2 respectively with no significant difference between the 2 groups ($P=0.17$). Significant improvement in VA was noted during treatment for each group. VA increased by 0.39 LogMAR units in group 1 ($P=0.00$) and 0.35 LogMAR units in group 2 ($P=0.00$). There was no statistically significant difference between the two groups considering improvement in VA ($P=0.33$).

In pyrimethamine/sulfadiazine group lesion size reduced from 972.22 before treatment to 311.11 micrometers after treatment. In azithromycin group lesion size changed from 862.50 micrometers to 507.64 μm after treatment in a 6-week follow-up period (Table 2). There was no significant difference between the 2 treatment groups in terms of retinal lesion size reduction. There was a significant efficacy of treatment in both groups regarding the reduction in the size of lesion and sharpening of borders (mean initial and final retinal lesion sizes as well as their reductions are shown separately for each group in Table 2) (Figure 1). No treatment failure was documented in any groups.

During the 24 months of follow-up period, 22 cases experienced one episode of recurrence (4 [11.1%] of patients in group 1 and 18 [50%] patients in group 2 [$P=0.00$]), indicating significant difference between two treatment groups. All recurrences occurred during the first 6 to 12 months of diagnosis In pyrimethamine/sulfadiazine group, compared with azithromycin group in which 4 patients (11.1%) experienced recurrence of the disease in 6 to 12 months and 14 patients (38.9%) in 12 to 24 months. Only one recurrence occurred in both groups and all of the recurrences were treated with initial medication.

Twenty patients in pyrimethamine/sulfadiazine group had poor tolerance to treatment due to gastrointestinal symptoms in 16 and dizziness in 4. However, no severe adverse reactions such as bone marrow suppression were observed in patients receiving pyrimethamine/sulfadiazine treatment. In group 2 Only 4 cases experienced adverse drug reaction, as a gastrointestinal symptoms (Table 1). So in intervention group (azithromycin-containing regimen) tolerance was much better than the other ($P=0.00$).

Discussion

Toxoplasma gondii, an obligate intracellular protozoan,

Table 1. The Initial Epidemiological and Clinical Characteristics of Cases in Each Group

	Pyrimethamine/Sulfadiazine Group (n = 36)	Azithromycin Group (n = 36)	*P* Value
Male	20 (55.4%)	18 (50%)	0.637
Female	16 (44.6%)′	18 (50%)	0.637
Age (y)	37.56 (20-60)	41.94 (27-56)	0.129
VA before treatment	0.73 log MAR (20/107 Snellen acuity)	0.82 log MAR (20/132 Snellen acuity)	0.49
VA after treatment	0.33 logMAR (20/42 Snellen acuity)	0.46 logMAR (20/57 Snellen acuity)	0.17
Improvement in VA	0.39 logMAR (20/49 Snellen acuity)	0.35 logMAR (20/44 Snellen acuity)	0.33
Positive IgG titer	140	166.4	0.54
Recurrence during 24 months after treatment	4 (11.1%)	18 (50%)	0.00
Adverse drug reaction	20 (55.5%)	4 (12.5%)	0.00

Table 2. Retinal Lesion Size Measurements in Two Groups Before And After Treatment

Retinal Lesion Size (μm)	Pyrimethamine/Sulfadiazine Group (n=36)	Azithromycin Group (n=36)	*P* Value
Before treatment	972.22	862.50	0.632
After treatment	311.11	507.64	0.086
Reduction during treatment	638.89	354.86	0.098

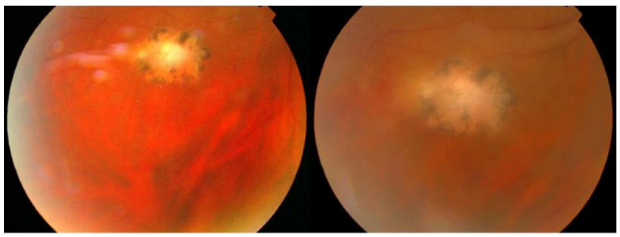

Figure 1. Fundus Photography of a Patient Before (right) and After (left) Treatment With Azithromycin.

is a leading cause of preventable visual loss particularly in young people (1). It infects almost 33% of the world's population (2). In a previous study conducted in tertiary center in Iran, *T. gondii* was recognized as a prevalent cause of posterior uveitis, accounting for 54.5% of all cases(4). This infection was characterized by necrotizing retinochoroiditis, scar formation and decreased vision.

Although valuable studies have been performed for OT highlighting the treatment protocols and their efficacy but no clinical trial has specifically compared with standard treatment in Iran. It seems necessary to study the efficacy and potential side effects of azithromycin regimen considering geographical differences. The aim of this study is to compare the efficacy of azithromycin with the pyrimethamine/sulfadiazine in the treatment of active, non-vision threatening chorioretinal toxoplasmosis in Nikukari eye hospital, Tabriz, Iran. The main outcome measures in evaluating success of treatment are disease recurrence and drug side effects.

OT has a variety of clinical presentations. It can also have a self-limited course of disease. These factors make the comparison of therapeutic choices in chorioretinal toxoplasmosis a challenge (11, 14). So decision making for ideal treatment for OT based on clinical study is difficult. Therefore, we employed a precise randomization and strict inclusion and exclusion criteria to eliminate hostage, parasitic and environmental confounding factors.

Nowadays combination of pyrimethamine/sulfadiazine is the standard treatment for OT based on the study results reported so far; however, low tolerance for this combination with adverse drug reactions, prompt researchers to look for alternatives with higher compliance and lower side effects.

The efficacy of azithromycin as a therapeutic option in *T. gondii* infections has been reported by many studies. Despite these evidences, we preferred to investigate the efficacy and clinical outcome of azithromycin only in non-vision threatening toxoplasmic retinochoroiditis versus standard treatment with pyrimethamine/sulfadiazine. We decided that the reduction of lesion size and sharpening of lesion borders may be a more suitable primary outcome for the evaluation of treatment efficacy. On the other hand, because we designed this trial for non-vision threatening cases, we included patients with no macular threatening lesions; therefore changes in VA (that mainly depends on relative location of lesion from macula) are not a significant outcome for judgment about treatment efficacy in this study.

In our study monotherapy with azithromycin appeared to be equally effective as classic treatment (pyrimethamine/sulfadiazine) for active non-vision threatening toxoplasmic chorioretinitis in terms of lesion size reduction, scarring and disease inactivity (Figure 1). On other hand azithromycin monotherapy regimen, versus the standard treatment with pyrimethamine/sulfadiazine, has a low rate of side effects with better compliance; despite higher recurrence.

A study by Rothova et al failed to show the efficacy of azithromycin versus standard treatment; however they indicated that it may be an effective alternative choice only for patients with low compliance for classic treatment (15). Bosch-Driessen et al in a prospective randomized study showed that azithromycin when used as a combination with pyrimethamine has efficacy, with lower adverse drug reactions (16).

Balaskas et al demonstrated that monotherapy with azithromycin for active, non-vision threatening OT requires a longer period of treatment versus classic regimen (but not statistically significant); however higher compliance reported subjectively by patients because of lower adverse reactions. Thus they introduced azithromycin as an appropriate alternative choice for non-vision threatening toxoplasmic chorioretinitis (11).

None of the previous researches reported a major adverse reaction of azithromycin, while high rate of bone marrow suppression(17) or other severe adverse drug reactions (11) were reported in some studies by pyrimethamine/sulfadiazine.

In our study no treatment failure was observed. Although Balaskas et al hypothesized several causes for treatment failure, including resistant nature of protozoan or low tolerance to medication (11).

In conclusion considering an increased interest for alternative choices for toxoplasmic chorioretinitis, this study introduced azithromycin monotherapy (as an inexpensive and available regimen) as an alternate treatment with equal efficacy, higher compliance and lower side effects than standard treatment. Our study has certain limitations. First, short time of follow-up and second absence of placebo controlled group. Furthermore,

limited number of patients, due to strict inclusion and exclusion criteria could be a shortcoming for our study. So we recommend more randomized placebo controlled clinical trials with longer time of follow-up and larger cases to evaluate the efficacy of azithromycin monotherapy opposing standard treatment and placebo.

Ethical Issues

This study was approved by the review board ethics committee of the training hospital and Tabriz University of Medical Sciences, Tabriz, Iran. Before recruitment, the study design and its probable safety and efficacy were explained for all of patients and informed consent was obtained.

Conflict of Interests

The authors do not have any conflict of interest.

Acknowledgements

The authors would like to express their deepest gratitude to all patients in our study and our heartfelt thanks go to the Nikookari hospital health workers.

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