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## Azithromycin versus Sulfadiazine and Pyrimethamine for non-vision-threatening toxoplasmic retinochoroiditis: A pilot study

### Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
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### Summary

#### Background:

The purpose of this pilot study is to compare the efficacy and tolerance of azithromycin alone as opposed to standard treatment with sulfadiazine and pyrimethamine for active, non-vision-threatening toxoplasmic retinochoroiditis.

#### Material/Methods:

We conducted a prospective, randomized, institutional clinical study comparing azithromycin to sulfadiazine and pyrimethamine for active, non-vision-threatening toxoplasmic retinochoroiditis. Nineteen out of 75 patients fulfilled inclusion criteria and were randomized into 2 treatment regimens. Nine patients were treated with sulfadiazine and pyrimethamine and 10 patients with azithromycin at a dose of 500 mg qd. Main outcome measures assessed were time to sharpening of lesion borders, time to lesion scarring, time to disease inactivity, and treatment tolerance.

#### Results:

Azithromycin monotherapy achieved lesion scarring and disease inactivity in all but 1 patient. Although no statistically significant difference was found between the 2 patient groups as regards main outcome measures for treatment efficacy, all median times to endpoints (days) were longer for the azithromycin group – time to sharpening of lesion borders on clinical evaluation (25.5 *vs.* 24) and masked evaluation of photographs (30.5 *vs.* 24), time to lesion scarring on clinical evaluation (73 *vs.* 47) and masked evaluation of photographs (71.5 *vs.* 36) and time to disease inactivity (73 *vs.* 49). Treatment tolerance was significantly better for the azithromycin group ( $p=0.0005$ ).

#### Conclusions:

Azithromycin monotherapy at a dose of 500 mg per day was shown to be effective and well-tolerated for the treatment of active, non-vision-threatening toxoplasmic retinochoroiditis. Duration of treatment was clinically longer for the azithromycin group.

#### key words:

**Azithromycin • inflammation • retina • toxoplasmosis • uveitis**

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## BACKGROUND

*Toxoplasma gondii* (*T. gondii*) can be considered a successful parasite in view of its worldwide distribution and broad range of hosts. Toxoplasmic retinochoroiditis constitutes the most common type of posterior uveitis in otherwise healthy individuals, both in tertiary referral centers and in community-based practices [1].

Substantial variations may be observed as regards the course of ocular toxoplasmic infection. While immunocompetent patients will almost invariably have only 1 focus of active retinochoroiditis, irrespective of the number of scars, a multifocal pattern of disease manifestation in 1 or both eyes is more common in immunocompromised individuals [2]. Larger lesions are usually associated with longer disease duration and an increased risk of complications [3].

The highly variable severity of ocular toxoplasmosis raises significant issues regarding appropriate therapeutic strategies, and even the need for any treatment at all, in this self-limiting disease [4]. However, ocular toxoplasmosis can lead to severe visual impairment and an update of current practices in the management of the disease by Holland et al. [5] revealed a trend towards more aggressive treatment, with twice as many ophthalmologists intending to treat all cases. The majority of clinicians adhered to the "classical" approach, with discrete courses of systemic drug therapy at times of active retinochoroiditis, using combinations of multiple antiparasitic drugs and corticosteroids. For patients, particularly those with sight-threatening lesions located near the optic disc or the fovea, the combination of sulfadiazine and pyrimethamine remains the treatment of choice and has been considered the standard against which other regimens should be evaluated [5]. However, the potential toxicity of, or intolerance to, this drug combination has prompted research for alternative treatment regimens with better adverse events profiles.

Azithromycin is an acid-stable, orally administered macrolide antibiotic, structurally related to erythromycin, with a similar antimicrobial spectrum [6]. *In vitro* and *in vivo* efficacy of azithromycin against *T. gondii* has been demonstrated in several animal models, as well as for the treatment of *T. gondii* encephalitis in patients with AIDS [7–16]. The efficacy of azithromycin alone [17] or in combination with pyrimethamine [18] and trimethoprim/sulfamethoxazole [19] in the management of active toxoplasmic retinochoroiditis has been demonstrated in previous studies. However, there has been no prospective randomized study comparing the efficacy of azithromycin alone versus a combination of sulfadiazine and pyrimethamine for the treatment of active toxoplasmic retinochoroiditis.

The purpose of this prospective, randomized pilot study is to compare the efficacy and tolerance of azithromycin alone versus the "classical" treatment regimen containing pyrimethamine and sulfadiazine, for the management of non-vision-threatening active toxoplasmic retinochoroiditis.

## MATERIAL AND METHODS

We conducted a prospective, randomized, intention-to-treat, pilot study comparing the efficacy and tolerance of 2 treatment regimens for active, non-vision-threatening toxoplasmic

retinochoroiditis. Inclusion criteria consisted of ambulatory patients of both sexes, of more than 18 years of age at the time of diagnosis, presenting with an active, creamy-white focal retinal lesion, associated or not with an adjacent hyper-pigmented chorioretinal scar, in accordance with the clinical criteria established by Holland et al. [20]. Efficient contraception was mandatory for all female patients during treatment and for 6 months thereafter. Written informed consent was obtained from all patients.

Exclusion criteria included the presence of a toxoplasmic lesion less than 400  $\mu\text{m}$  from the center of the macula or the optic disc; the presence of any other ocular morbidities; history of immunosuppressive, corticosteroid or antiviral treatment within 14 days prior to inclusion in the study; known intolerance to any agent involved in the treatment regimens; patients with best corrected visual acuity of less than 1/120 on the Snellen chart in either eye; patients with known auditory defects, pregnancy, breast-feeding, or diabetes; and concomitant treatment with any 1 of the following agents: ergotamine, fluconazole, cyclosporine, digoxin, rifabutin or anti-coagulant medication.

Serum anti-*T. gondii* IgG and IgM antibodies were determined in all patients and found to be consistent with the clinical diagnosis of active toxoplasmic retinochoroiditis.

Patients were randomly assigned to 1 of the treatment arms (random choice by the patient of a sealed envelop containing the treatment regimen), consisting of either a combination of pyrimethamine (25 mg bid) and sulfadiazine (1000 mg tid for patients weighing less than 65 kg or 1000 mg qid for those weighing more than 65 kg) associated with folic acid (15 mg qd) or azithromycin alone (500 mg qd). In addition, all patients were treated with prednisone 1 mg/kg/day initiated 3 days after the beginning of antiparasitic treatment with gradual tapering off by 5 mg every 3 days.

Patients were examined on day 1 and then every  $15\pm 5$  days until disease inactivity. A further visit at 3 months from the beginning of treatment was performed for all patients. Any discomfort or adverse events were recorded. Patients were shown a numbered ruler (visual analogue score) and were asked to name and show the grading that best matched their level of comfort with treatment (0 – highest imaginable discomfort, 10 – no discomfort). On each visit, clinical assessment included visual acuity, slit-lamp biomicroscopy with grading of inflammatory reaction in the anterior chamber and vitreous according to the SUN classification, tonometry, dilated fundus examination, and automated laser flare photometry (Kowa Laser Flare Meter FM-600). The time points of sharpening of lesion borders, of lesion scarring, and of disease inactivity, defined as a pigmented lesion with sharp borders and the absence of any inflammatory activity from the anterior chamber and the vitreous, were also noted. Treatment was discontinued as soon as disease was deemed inactive based on clinical evaluation. Fundus photographs of the retinochoroidal lesion were taken on every visit. Fluorescein and indocyanine-green angiography following a standard protocol for posterior uveitis were performed on the initial visit and at the time point when disease inactivity was observed.

Laboratory examinations at baseline included complete blood count, serum glucose levels and renal and liver

**Table 1.** Features of the patient sample at randomization in both treatment arms.

|                                | Group Azithromycin | Group Sulfadiazine/<br>Pyrimethamine | p*         |
|--------------------------------|--------------------|--------------------------------------|------------|
|                                | N=10               | N=9                                  |            |
| <b>Continuous variables</b>    | <b>Mean ±SD</b>    | <b>Mean ±SD</b>                      |            |
| Age (years)                    | 40.9±17.1          | 47.7±19.1                            | 0.595      |
| Symptoms duration (days)       | 14.6±19.1          | 8.6±9.6                              | 0.412      |
| Lesion size (mm <sup>2</sup> ) | 6.3±4.5            | 9.2±5.1                              | 0.121      |
| BCVA at presentation (logMAR)  | 0.18±0.15          | 0.18±0.19                            | 0.934      |
| <b>Categorical variables</b>   | <b>n (%)</b>       | <b>n (%)</b>                         | <b>p**</b> |
| Male sex                       | 7 (70.0)           | 4 (44.4)                             | 0.370      |
| Primary lesion                 | 5 (50.0)           | 3 (33.3)                             | 0.650      |

\* value from Mann-Whitney-Wilcoxon test for independent samples; \*\* value derived from Fisher's exact test; BCVA – best-corrected visual acuity.

biochemistry. A complete blood count was also performed on each visit for patients in the sulfadiazine/pyrimethamine treatment arm.

Fundus photographs were evaluated in a masked fashion by an independent ophthalmologist (KB). The time points of sharpening of lesion borders and of lesion scarring were recorded. Initial and final lesion size was measured using the appropriate application of the Imagenet software (TOPCON IMAGENet i-base Basic version: 3.5.5) on fluorescein angiography, both on initial visit and at the time point of disease inactivity. Late frames at 10 minutes were used for these measurements for all patients. Change in lesion size was calculated from these measurements.

The criterion for failure of treatment was an increase in lesion size by more than 20% during the course of treatment, confirmed by evaluation of fundus photographs. In the case of treatment failure under azithromycin, patients would be switched to the standard regimen with sulfadiazine and pyrimethamine. Criteria for treatment discontinuation were evidence of bone marrow depression on complete blood count (leucocyte count below 4,000/ml, platelet count below 150,000/μl), a skin rash, or any other allergic reaction known to be potentially attributable to investigated treatment agents.

Statistical analysis was performed for the comparison of the 2 groups of patients as regards baseline parameters and main outcome measures. We compared continuous variables with Mann-Whitney-Wilcoxon test and categorical variables with Fisher's exact test. Adjusted p-values for multiple comparisons were also sought. Statistical level of significance was assigned for P values lower than 0.05.

Main outcome measures were percentage change in lesion size after treatment; time to sharpening of lesion borders on clinical evaluation and on masked evaluation of photographs; time to lesion scarring on clinical evaluation and on masked evaluation of photographs; time to disease inactivity; treatment tolerance; and treatment intolerance leading to discontinuation of treatment.

The Bland-Altman method was employed to calculate the mean difference and 95% limits of agreement between the 2 methods of measurement of time to lesion scarring (clinical evaluation and masked evaluation of fundus photographs).

Statistical analysis was performed with StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP.

Institutional Review Board (IRB)/ Ethics Committee approval of the University of Lausanne was obtained. The described research adhered to the tenets of the Declaration of Helsinki (Protocol 26/03, Ethics Committee of the University of Lausanne). Swissmedic notification was performed for patients 14 to 19 according to Swiss regulations.

## RESULTS

Out of 75 consecutive patients presenting with active toxoplasmic retinochoroiditis to the Uveitis Clinic of the Jules Gonin Eye Hospital over a 7-year period, 19 patients fulfilled the criteria for inclusion in the study; 13 patients were excluded because they were under 18 years of age at the time of diagnosis, 10 had lesions close to the macula, 10 had lesions close to the optic disc, 7 patients declined participation in the study, 6 were already being treated at the time they presented to our department, 3 patients had serious systemic comorbidities, 2 had known allergy to pyrimethamine, 2 had 1 eye with visual acuity below 1/120 on the Snellen chart, there was 1 diabetic patient and 2 patients with known substantial auditory defect.

The epidemiological and clinical characteristics of the study sample at randomization are presented in Table 1. Nineteen patients were included in the study. Nine patients were randomized to the treatment regimen containing sulfadiazine/pyrimethamine and 10 to the regimen containing azithromycin. At randomization, no statistically significant difference as regards age, sex, symptom duration prior to initiation of treatment, initial lesion size, BCVA at presentation or the presence of primary retinal lesions was found between the 2 treatment arms.

**Table 2.** Comparison of main outcome measures between the two groups.

|   | Group Azithromycin |         | Group Sulfadiazine/<br>Pyrimethamine |         | p*      |
|---|--------------------|---------|--------------------------------------|---------|---------|
|   | N=10               |         | N=9                                  |         |         |
| <b>Continuous variables</b>             | Median (IQR)       |         | Median (IQR)                         |         | p**     |
| Change in lesion size                   |                    |         |                                      |         |         |
| (mm <sup>2</sup> )                      | -1,695.0           | (2.325) | -3.51                                | (3.222) | 0.072   |
| (%)                                     | -44.4              | (26.10) | -56.6                                | (24.40) | 0.248   |
| Time to sharpening of lesion borders    |                    |         |                                      |         |         |
| clinical evaluation (days)              | 25.5               | (23.00) | 24.0                                 | (13.50) | 0.870   |
| masked evaluation of photographs (days) | 30.5               | (30.75) | 24.0                                 | (17.00) | 0.270   |
| Time to lesion scarring                 |                    |         |                                      |         |         |
| clinical evaluation (days)              | 73.0               | (57.25) | 47.0                                 | (14.00) | 0.236   |
| masked evaluation of photographs (days) | 71.5               | (57.50) | 36.0                                 | (25.50) | 0.307   |
| Time to disease inactivity (days)       | 73.0               | (61.25) | 49.0                                 | (42.50) | 0.540   |
| Treatment tolerance (VAS score)         | 8.5                | (5.00)  | 3.0                                  | (4.00)  | 0.0005  |
| <b>Categorical variables</b>            | n (%)              |         | n (%)                                |         | p**     |
| Treatment Failure                       | 1.0                | (10.00) | 0.0                                  | (0.00)  | >0.999F |

\* value from Mann-Whitney-Wilcoxon test for independent samples; \*\* value derived from Fisher's exact test; IQR – inter-quartile range; VAS – visual analogue score.

All the patients on sulfadiazine/pyrimethamine and all but 1 patient on azithromycin exhibited favorable response to treatment, with lesion scarring and disease inactivity. With respect to main outcome measures of treatment efficacy, median times to specific end-points (sharpening of lesion borders, lesion scarring and disease inactivity) were longer in a clinically significant way for the azithromycin group, both on clinical evaluation and on masked evaluation of photographs, as summarized in Table 2. Median time to lesion scarring on masked evaluation of photographs was 71.5 days (interquartile range (IQR) 57.5) for azithromycin versus 36 days (IQR 25.5) for sulfadiazine/pyrimethamine, while time to disease inactivity was 73 days (IQR 61.25) versus 49 days (IQR 42.5), respectively. However, none of the differences in the above times reached statistical significance. Demonstrating statistical non-inferiority between the 2 treatment regimens would require a considerably larger sample size. Interestingly, no statistically significant difference was observed concerning total prednisone dose/ body weight received by patients in the 2 treatment arms ( $p=0.185$ ). The adjusted  $p$ -values for multiple comparisons yield similar results in terms of statistical significance. On the other hand, overall treatment tolerance was much better for patients who received the azithromycin-containing regimen ( $p=0.0005$ ), with a median treatment tolerance of 8.5 on the visual analogue score (VAS) for the azithromycin group as opposed to 3 for the sulfadiazine/pyrimethamine group.

All patients were included in the analysis as appropriate in an intention-to-treat model, including the single patient

on azithromycin that failed to respond to treatment and was eventually switched to the combination of sulfadiazine and pyrimethamine. Time to specific end-points was therefore significantly higher for that patient in comparison to all other patients in the analysis (time to disease inactivity of 235 days).

The Bland-Altman method revealed that the differences of measurements, within  $\pm 1.96$  standard deviations, of time to lesion scarring between the 2 methods used (clinical evaluation and masked evaluation of fundus photographs) were not clinically important; therefore the 2 methods can be used interchangeably. This fact signifies the lack of a possible bias introduced by unmasked clinical evaluation in the context of the present study.

In terms of adverse events, 1 patient developed a skin rash 45 days after treatment initiation with sulfadiazine/pyrimethamine. As a consequence, treatment was discontinued at that point, which coincided with disease inactivity for that particular patient. All patients treated with sulfadiazine/pyrimethamine reported weak treatment tolerance, with symptoms including malaise, dizziness, headaches and gastrointestinal disorders. However, no major adverse events such as bone marrow depression were observed in patients receiving sulfadiazine/pyrimethamine.

Treatment failure was documented in 1 patient in the azithromycin arm. Over the course of treatment, that patient exhibited persistence of inflammatory reaction and progressive increase in lesion size, with no signs of scarring.

Seventy-two days after the initiation of treatment, the patient was switched to sulfadiazine/pyrimethamine, with eventually favorable clinical response.

All patients were included in the statistical analysis in an intention-to-treat approach. However, no statistically significant difference in treatment failure rate could be identified between the 2 treatment groups. ( $p>0.999$ )

## DISCUSSION

Azithromycin monotherapy appeared to be an efficient treatment option for non-vision-threatening toxoplasmic retinochoroiditis leading to lesion scarring and disease inactivity in all but 1 patient. Disease remission required longer duration of treatment with azithromycin as opposed to sulfadiazine/pyrimethamine in a clinically, but not statistically, significant way. On the other hand, treatment tolerance was significantly better in the azithromycin arm of the study.

Any attempt to compare therapeutic options for ocular toxoplasmosis is subject to substantial difficulties stemming from the self-limiting nature of the disease. A combination of host, parasite and environmental factors influences severity of disease presentation, making it difficult to clearly identify the characteristics of the ideal drug for ocular toxoplasmosis [2]. A strict randomization process, as employed in this study, is required to eliminate the effect of potential confounding factors such as age [21].

The ability of any treatment regimen to alter the natural history of toxoplasmic retinochoroiditis has not been unequivocally demonstrated so far. In a systematic review of the literature by Stanford et al, only 3 prospective, randomized, placebo-controlled clinical trials for the treatment of ocular toxoplasmosis in immunocompetent patients could be identified [22]. None of these studies clearly confirmed the efficacy of short-term drug therapy for active toxoplasmic retinochoroiditis. However, clinical observation and experience have led uveitis specialists to consider the potential benefits of treating ocular toxoplasmosis in terms of reduction in lesion size and disease duration.

Several studies have attempted to assess the efficacy of various antiparasitic drug combinations in the treatment of ocular toxoplasmosis. Investigated agents include currently used treatment options for toxoplasmic retinochoroiditis, such as pyrimethamine and sulfadiazine, clindamycin per os [23–25] and intravitreal [26], trimethoprim-sulfamethoxazole [19,27], atovaquone [28,29] or various combinations of the above and even quadruple therapy (30). Corresponding studies claimed to shorten the duration of active disease in toxoplasmic retinochoroiditis. However, different study designs, absence of controls and substantial variation in the choice of outcomes for the evaluation of treatment efficacy render the comparison of these studies difficult.

The best clinical results reported so far in the management of ocular toxoplasmosis involve the combination of pyrimethamine and sulfadiazine [31]. Both sulfadiazine and pyrimethamine interfere at distinct stages of the folate cycle, thus enhancing their common action. Their synergistic activity in ocular toxoplasmosis has been documented in animal models, rendering this combination most effective

and recommended for the treatment of vision-threatening toxoplasmosis [31]. Similar mechanism of action, however, leads to analogous adverse effects, such as bone marrow depression. Potential weak tolerance of this antiparasitic combination prompted investigators to look for alternative therapeutic options with less adverse effects.

The role of azithromycin as a therapeutic agent in infections with *T. gondii* has been supported by several studies and has proven effective in the treatment of active toxoplasmosis in several animal models [16]. Azithromycin alone or in combination with pyrimethamine has beneficial effects for the treatment of toxoplasmic encephalitis in patients with AIDS, is well tolerated in adults and children, and has a low incidence of adverse events [32].

Few reports deal with azithromycin in the management of ocular toxoplasmosis. A pilot study showed a favorable response, defined as waning of initial inflammation within 4 weeks after treatment initiation, to a 5-week course of azithromycin in 7 out of 11 patients presenting with active toxoplasmic retinochoroiditis in various locations [17]. In a prospective, randomized trial of pyrimethamine and azithromycin versus pyrimethamine and sulfadiazine for the treatment of sight-threatening ocular toxoplasmosis [18], the efficacy of a short-term multidrug regimen containing azithromycin was similar to standard therapy, with significantly fewer and less severe adverse events in the azithromycin-containing treatment group.

A randomized controlled study appeared essential to better define the therapeutic role of azithromycin monotherapy in ocular toxoplasmosis. Despite substantial evidence of the efficacy of azithromycin against *T. gondii*, we deemed it insufficient to support the treatment of vision-threatening toxoplasmic retinochoroiditis with azithromycin alone. We therefore preferred to include patients with non-vision-threatening toxoplasmic retinochoroiditis and to compare the efficacy of azithromycin versus classic therapy in this group of patients. The potential benefits for patients from documenting the efficacy of azithromycin for the treatment of ocular toxoplasmosis include a simpler treatment regimen with fewer pills per day, better tolerability and fewer adverse events.

In accordance with Bosch-Driessen et al. [18], we chose a dosage of azithromycin based on 2 *in vitro* studies, showing that concentration of azithromycin in brain tissue of patients with brain tumors 48 hours after the administration of 500 mg of azithromycin reached a level of  $3.64\pm 3.81$   $\mu\text{g/g}$  [33,34]. This value is between the IC 50 and IC 90 (50% and 90% inhibitory concentrations, respectively) for parasite growth in the presence of pyrimethamine. However, this concentration of azithromycin barely reached the IC 50 for parasite growth when used alone in the same study [34]. The study by Tseng et al. [35] for the treatment of a *Mycobacterium avium* complex infection in HIV+ patients with azithromycin at a dose of 600 mg per day revealed a 17% incidence of ototoxicity. The dosage used in our study was therefore supposed to allow sufficient tissue concentrations of azithromycin, while assuring a decreased risk of adverse events, notably ototoxicity. The dosage of sulfadiazine/pyrimethamine that was chosen matched the common practices of a majority of clinicians [36].

Although 1 or several clinically-relevant surrogates of treatment efficacy have yet to be determined in toxoplasmic retinochoroiditis, we agree with Holland [37] that the time interval to sharpening of lesion borders and the time interval to disease inactivity may be more appropriate primary outcome measures for treatment efficacy. Visual acuity, on the other hand, is not a reliable outcome measure, largely depending on lesion location. In particular, since the present study included only non-vision-threatening lesions, change in visual acuity at the end of follow-up yields less valuable information in terms of treatment efficacy.

Although patients on azithromycin monotherapy exhibited response to treatment with eventual lesion scarring and disease inactivity, clinical observation revealed a significantly increased duration of treatment for these patients as opposed to the group treated with sulfadiazine/pyrimethamine. This increased duration of treatment with azithromycin could not be statistically verified in view of the small study sample. Differences in initial lesion size may also in part justify this discrepancy, as they significantly influence the duration of treatment in toxoplasmic retinochoroiditis. In the context of the present pilot study, sample size would not allow for establishing non-inferiority between the 2 treatment regimens. Although a strong statistically significant difference in outcome measures of treatment efficacy would indeed point to true differences in efficacy between the 2 treatment regimens, the absence of such statistically significant differences cannot convincingly establish the equivalence of the 2 regimens. Despite longer treatment duration, no significant adverse events or patient discomfort with treatment were identified for the azithromycin group.

None of the previously described severe adverse events of the standard treatment regimen of sulfadiazine/pyrimethamine was observed, in contrast to the high rate of bone marrow depression reported in other studies [3,38]. Minor adverse effects of this regimen were, on the other hand, rather common, leading to a statistically significant difference in treatment tolerance and patient comfort with treatment between the 2 arms of the study. In contrast, azithromycin was well tolerated by all patients, with no minor or major adverse events observed.

One patient treated with azithromycin failed to respond to treatment. Although several causes for such a phenomenon could be hypothesized, including infection with a resistant strain of *T. gondii*, poor compliance to treatment is the most likely explanation. On the other hand, the rate of treatment failure was not statistically significantly different between the 2 treatment arms. This patient was also included in the statistical analysis in an intention-to-treat approach. Such an analysis allows for circumventing a potential bias arising from the exclusion of patients with poor response to investigated treatment.

This study has certain limitations. Given that this is a first attempt to evaluate the efficacy of azithromycin alone for the management of ocular toxoplasmosis, the inclusion criteria chosen were strict, thus limiting the number of recruited patients. A meaningful limitation of the present study resides in the small numbers, rendering proper non-inferiority statistics inapplicable. Significantly higher numbers, however, are unlikely to be achieved in the context of posterior uveitis,

especially on an institutional basis. Fair conclusions of the present study would therefore be that azithromycin monotherapy is efficient for the treatment of non-vision-threatening toxoplasmic retinochoroiditis, while being significantly better tolerated than sulfadiazine/pyrimethamine, and that treatment duration appeared clinically to be longer for the azithromycin group. Proposed statistical associations concerning the comparison of the 2 treatment regimens in respect to efficacy are to be considered merely descriptive. Further limitations of the present study include the absence of a placebo-controlled arm and the fact that both examiners and patients were unmasked to treatment; these factors may influence interpretation of drug adverse events and may affect the identification of the time points of lesion scarring and disease inactivity. To offset this limitation, a masked evaluation of fundus photographs by an independent ophthalmologist was performed in order to minimize bias that could arise from unmasked clinical evaluation. The statistical comparison of measurements obtained by clinical evaluation and masked evaluation of photographs did not reveal a clinically important disparity of the 2 methods.

## CONCLUSIONS

Azithromycin alone for active, non-vision-threatening toxoplasmic retinochoroiditis led to disease remission in all but 1 case, although requiring a longer duration of treatment as opposed to sulfadiazine/pyrimethamine. Additionally, subjective reporting of adverse events by patients showed that azithromycin was much better tolerated. Therefore, azithromycin may be a valuable and reasonable alternative in the management of active, non-vision-threatening toxoplasmic retinochoroiditis. Given the increased interest in the use of azithromycin for toxoplasmic retinochoroiditis observed in recent years, this pilot study offers valuable evidence in support of the inclusion of azithromycin in the pharmaceutical armamentarium against ocular toxoplasmosis. Whether better treatment tolerance of azithromycin is adequate an advantage to offset the need for longer duration of treatment is open for debate. A multicenter trial would serve to verify and refine these findings.

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## Conflict of interest

None of the authors have any financial or property interest on any product, method or material presented in this paper. No conflicting relationship exists for any author.

## REFERENCES:

1. McCannel CA, Holland GN, Helm CJ et al: Causes of uveitis in the general practice of ophthalmology. UCLA Community-Based Uveitis Study Group. *Am J Ophthalmol*, 1996; 121: 35–46
2. Holland GN: Ocular toxoplasmosis: a global reassessment. Part II: disease manifestations and management. *Am J Ophthalmol*, 2004; 137: 1–17

3. Rothova A, Meenken C, Buitenhuis HJ et al: Therapy for ocular toxoplasmosis. *Am J Ophthalmol*, 1993; 115: 517–23
4. de-la-Torre A, Stanford M, Curi A et al: Therapy for ocular toxoplasmosis. *Ocul Immunol Inflamm*. 2011, 19(5): 314–20
5. Holland GN, Lewis KG: An update on current practices in the management of ocular toxoplasmosis. *Am J Ophthalmol*, 2002; 134: 102–14
6. Peters DH, Friedel HA, McTavish D: Azithromycin. A review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. *Drugs*, 1992; 44: 750–99
7. Costa IN, Angeloni MB, Santana LA et al: Azithromycin inhibits vertical transmission of *Toxoplasma gondii* in *Calomys callosus* (Rodentia: *Cricetidae*). *Placenta*, 2009; 30: 884–90
8. Tabbara KF, Hammouda E, Tawfik A et al: Azithromycin prophylaxis and treatment of murine toxoplasmosis. *Saudi Med J*, 2005; 26: 393–97
9. Lescano SA, Amato NV, Chieffi PP et al: [Evaluation of the efficacy of azithromycin and pyrimethamine, for treatment of experimental infection of mice with *Toxoplasma gondii* cystogenic strain]. *Rev Soc Bras Med Trop*, 2004; 37: 460–62
10. Degerli K, Kilimcioglu AA, Kurt O et al: Efficacy of azithromycin in a murine toxoplasmosis model, employing a *Toxoplasma gondii* strain from Turkey. *Acta Trop*, 2003; 88: 45–50
11. Jacobson JM, Hafner R, Remington J et al: Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplastic encephalitis in AIDS. *AIDS*, 2001; 15: 583–89
12. Wiselka MJ, Read R, Finch RG: Response to oral and intravenous azithromycin in a patient with toxoplasma encephalitis and AIDS. *J Infect*, 1996; 33: 227–29
13. Chang HR: The potential role of azithromycin in the treatment of prophylaxis of toxoplasmosis. *Int J STD AIDS*, 1996; 7(Suppl.1): 18–22
14. Derouin F, Almadany R, Chau F et al: Synergistic activity of azithromycin and pyrimethamine or sulfadiazine in acute experimental toxoplasmosis. *Antimicrob Agents Chemother*, 1992; 36: 997–1001
15. Farthing C, Rendel M, Currie B, Seidlin M: Azithromycin for cerebral toxoplasmosis. *Lancet*, 1992; 339: 437–38
16. Araujo FG, Gupta DR, Remington JS: Azithromycin, a macrolide antibiotic with potent activity against *Toxoplasma gondii*. *Antimicrob Agents Chemother*, 1988; 32: 755–57
17. Rothova A, Bosch-Driessen LE, van Loon NH, Treffers WF: Azithromycin for ocular toxoplasmosis. *Br J Ophthalmol*, 1998; 82: 1306–8
18. Bosch-Driessen LH, Verbraak FD, Suttorp-Schulten MS et al: A prospective, randomized trial of pyrimethamine and azithromycin vs pyrimethamine and sulfadiazine for the treatment of ocular toxoplasmosis. *Am J Ophthalmol*, 2002; 134: 34–40
19. Yazici A, Ozdal PC, Taskintuna I et al: Trimethoprim/Sulfamethoxazole and azithromycin combination therapy for ocular toxoplasmosis. *Ocul Immunol Inflamm*, 2009; 17: 289–91
20. Holland GN, O'Connor R, Belfort R, Remington JS: Toxoplasmosis. In: Pepose JS, Holland GN, Wilhelmus KR (eds.), *Ocular infection and immunity*. St. Louis: Mosby Year Book, Inc., 1996; 1183–23
21. Holland GN: Ocular toxoplasmosis: the influence of patient age. *Mem Inst Oswaldo Cruz*, 2009; 104: 351–57
22. Stanford MR, See SE, Jones LV, Gilbert RE: Antibiotics for toxoplasmic retinochoroiditis: an evidence-based systematic review. *Ophthalmology*, 2003; 110: 926–31
23. Tabbara KF, O'Connor GR: Treatment of ocular toxoplasmosis with clindamycin and sulfadiazine. *Ophthalmology*, 1980; 87: 129–34
24. Lakhanpal V, Schocket SS, Nirankari VS: Clindamycin in the treatment of toxoplasmic retinochoroiditis. *Am J Ophthalmol*, 1983; 95: 605–13
25. Colin J, Harie JC: [Presumed toxoplasmic chorioretinitis: comparative study of treatment with pyrimethamine and sulfadiazine or clindamycin]. *J Fr Ophthalmol*, 1989; 12: 161–65
26. Soheilian M, Ramezani A, Azimzadeh A et al: Randomized trial of intravitreal clindamycin and dexamethasone versus pyrimethamine, sulfadiazine, and prednisolone in treatment of ocular toxoplasmosis. *Ophthalmology*, 2011; 118(1): 134–41
27. Opremcak EM, Scales DK, Sharpe MR: Trimethoprim-sulfamethoxazole therapy for ocular toxoplasmosis. *Ophthalmology*, 1992; 99: 920–25
28. Pearson PA, Piracha AR, Sen HA, Jaffe GJ: Atovaquone for the treatment of toxoplasma retinochoroiditis in immunocompetent patients. *Ophthalmology*, 1999; 106: 148–53
29. Winterhalter S, Severing K, Stammen J et al: Does atovaquone prolong the disease-free interval of toxoplasmic retinochoroiditis? *Graefes Arch Clin Exp Ophthalmol*, 2010; 248(8): 1187–92
30. Lam S, Tessler HH: Quadruple therapy for ocular toxoplasmosis. *Can J Ophthalmol*, 1993; 28: 58–61
31. Nussenblatt RB, Whitcup SM, Palestine AG: Ocular Toxoplasmosis. In: Nussenblatt RB, Whitcup SM, Palestine AG, editors. *Uveitis. Fundamentals and clinical practice*. St. Louis: Mosby Year Book Inc., 1996: 211–28
32. Hopkins S: Clinical toleration and safety of azithromycin. *Am J Med*, 1991; 91: 40–45S
33. Jaruratanasirikul S, Hortiwakul R, Tantisarasant T et al: Distribution of azithromycin into brain tissue, cerebrospinal fluid, and aqueous humor of the eye. *Antimicrob Agents Chemother*, 1996; 40: 825–26
34. Cantin L, Chamberland S: *In vitro* evaluation of the activities of azithromycin alone and combined with pyrimethamine against *Toxoplasma gondii*. *Antimicrob Agents Chemother*, 1993; 37: 1993–96
35. Tseng AL, Dolovich L, Salit IE: Azithromycin-related ototoxicity in patients infected with human immunodeficiency virus. *Clin Infect Dis*, 1997; 24: 76–77
36. Lum F, Jones JL, Holland GN, Liesegang TJ: Survey of ophthalmologists about ocular toxoplasmosis. *Am J Ophthalmol*, 2005; 140: 724–26
37. Holland GN: Prospective, randomized trial of trimethoprim/sulfamethoxazole vs. pyrimethamine and sulfadiazine in the treatment of ocular toxoplasmosis: discussion. *Ophthalmology*, 2005; 112: 1882–84
38. Ghosh M, Levy PM, Leopold IH: Therapy of toxoplasmosis uveitis. *Am J Ophthalmol*, 1965; 59: 55–61