

# Azithromycin for ocular toxoplasmosis

Aniki Rothova, Lotje E H Bosch-Driessen, Ninette H van Loon, W Frits Treffers

## Abstract

**Aims**—To investigate the efficacy of azithromycin in patients with ocular toxoplasmosis.

**Methods**—11 immunocompetent patients with ocular toxoplasmosis were treated with azithromycin (500 mg the first day, followed by 250 mg/day for 5 weeks). Ocular and systemic examinations were performed during active retinitis episodes and all patients were followed for at least 1 year.

**Results**—The intraocular inflammation disappeared within 4 weeks in seven patients, including two cases with progressive retinitis despite previous treatment with pyrimethamine, sulphadiazine, and folic acid. Recurrence of retinitis occurred in three patients (27%) within the first year of follow up. No systemic side effects of azithromycin were encountered.

**Conclusion**—These results indicate that although azithromycin cannot prevent recurrent disease it may be an effective alternative for patients with ocular toxoplasmosis who cannot tolerate standard therapies.

(Br J Ophthalmol 1998;82:1306-1308)

The lack of effective therapy for ocular toxoplasmosis is responsible for the tragic loss of eyesight in this parasitic disease. Treatment, which has not changed essentially during the past few decades, consists of various combinations of antiparasitic drugs; the most common agents used are pyrimethamine, clindamycin, and the sulphonamides. These drugs are sometimes given in combination with corticosteroids to alleviate the inflammatory reaction.<sup>1</sup> The purpose of this approach is to stop retinal damage by hampering multiplication of the parasites during the active stage of retinitis.<sup>2</sup> However, tissue cysts remain resistant to all known forms of therapy so that recurrences cannot be prevented. Therefore, the potentially toxic treatment with pyrimethamine is indicated only in the event of active sight threatening disease.<sup>3</sup> The interpretation of data on therapeutic efficacy in a self limiting disease is extremely difficult; controlled studies have demonstrated that current antiparasitic treatments yield only a slight benefit.<sup>2,4</sup>

With the spread of AIDS, the frequency of severe disseminated toxoplasmosis in humans has risen; obviously there is an urgent need for more effective treatment. The search for better and less toxic antiparasitic drugs has yielded two serious candidates—the hydroxynaphthoquinone atovaquone and the azalide antibiotic azithromycin, both of which have exhibited in

vitro and in vivo efficacy not only against tachyzoite but also against cystic forms of *Toxoplasma gondii*.<sup>5</sup> The purpose of this open study was to investigate the use of azithromycin for treatment of ocular toxoplasmosis in immunocompetent patients.

## Methods

We treated 11 immunocompetent patients with ocular toxoplasmosis with azithromycin (500 mg the first day, followed by 250 mg/day for 5 weeks). The study population included three cases of progressive macular disease despite initial treatment with pyrimethamine, sulphadiazine, and folic acid. In three additional patients the toxicity of triple therapy with pyrimethamine necessitated discontinuation of these drugs. The remaining five patients, who had active toxoplasmic lesions located adjacent to large vascular arcades, refused combination therapy with pyrimethamine (four had taken these drugs previously). The diagnosis of toxoplasmosis was based on the clinical observation of unilateral focal necrotising retinitis associated with typical old pigmented scars and presence of specific IgG antibodies.<sup>3</sup> In seven patients, the diagnosis was confirmed by the intraocular antibody production and/or presence of *T gondii* DNA in polymerase chain reaction in intraocular fluid (intraocular fluid analysis was not performed for remaining four patients).<sup>6</sup> Any complications of therapies were carefully monitored; complete blood cell counts and renal and liver function tests were performed during the third or fourth week of treatment. All patients were followed for at least 1 year (average 20 months).

Treatment with azithromycin was considered effective when the intraocular inflammatory activity disappeared within 4 weeks and the retinal lesions became flat and sharply demarcated.

## Results

Seven patients exhibited a good response (Table 1, patients 1, 3, 5, 6, 8, 9, 11), including two with progressive retinitis for more than 8 weeks despite treatment with pyrimethamine, sulphadiazine, and folic acid (Table 1, patients 6 and 8). Four patients had an incomplete response; two of them received additional pyrimethamine on days 7 and 8, respectively (Table 1, patients 2 and 4). Despite this combined approach, both showed active intraocular disease at 4 weeks (one patient had persistent vitreous opacities with a quiescent retinal lesion and the other still had an active retinal lesion, which became ultimately quiet at week 8). The remaining two patients with an incomplete response had large retinal lesions and had previously been treated with pyrimethamine without effect (Table 1, patients 7

Department of  
Ophthalmology, FC  
Donders Institute,  
Academic Hospital  
Utrecht, Netherlands

A Rothova  
L E H Bosch-Driessen  
N H van Loon  
W F Treffers

Correspondence to:  
Aniki Rothova, MD,  
F C Donders Institute,  
Department of  
Ophthalmology, Academic  
Hospital Utrecht, PO Box 85  
500, 3508 GA Utrecht,  
Netherlands.

Accepted for publication  
15 April 1998

Table 1 Azithromycin for ocular toxoplasmosis

Patient No, sex, age (years)	Indication for treatment	Interval between onset and azithromycine medication (weeks)	Size of retinal lesion (DD)	Duration of retinitis (weeks)	Complications			Visual acuity			Retinitis recurrence (follow up, months)
					Systemic	Ocular	Additional treatment	Onset	Final	Follow up (months)	
1, M, 25	patient's choice	<1	1	3	—	increase of vitreous opacities	pyrimethamine and prednisone	20/50	20/20	21	—
2, M, 44	patient's choice	2	2.5	6	—	increase of vitreous opacities	pyrimethamine and prednisone	20/60	20/20	20	+ (5)
3, F, 24	patient's choice	<1	1	4	—	—	—	20/30	20/25	22	+ (6)
4, M, 43	patient's choice	<1	3	8	—	increase of vitreous opacities	pyrimethamine and sulphadiazine	20/60	20/20	20	—
5, F, 33	patient's choice	<1	1	3	—	—	—	20/30	20/20	20	—
6, M, 28	intolerant to triple treatment*	5	0.5	4	—	—	prednisone	20/200	20/25	21	—
7, F, 31	progressive disease with triple treatment*	>8	6	7	—	—	—	LP	LP†	20	—
8, F, 29	progressive disease with triple treatment*	>8	4	3	—	—	—	CF	20/200†	21	—
9, M, 54	progressive disease with triple treatment*	8	2	4	—	—	—	20/60	20/25	23	—
10, F, 73	intolerant to triple treatment*	3	3	5	—	—	—	HM	HM†	20	+ (7)
11, F, 69	intolerant to triple treatment*	2	1.5	4	—	—	—	CF	20/50	13	—

\*Triple treatment included pyrimethamine, sulphadiazine, prednisone, and leucovorin.

†Subnormal visual acuity was caused by large macular lesion and optic nerve atrophy (patient 7), optic nerve atrophy (patient 8) and by retinal artery occlusion (patient 10).

and 10); both exhibited persistent vitreous opacities 4 weeks after initiation of azithromycin. Their retinal lesions became inactive during the fifth and seventh weeks of follow up, respectively. Of six patients who received triple therapy with pyrimethamine immediately before azithromycin, four exhibited a good therapeutic response to azithromycin (Table 1, patients 6, 8, 9, 11). The patient (no 6) who had to discontinue pyrimethamine and sulphadiazine because of bone marrow depression and toxic dermatitis had a macular lesion in his only functioning eye. Subsequently, azithromycin was administered and the lesion became quiescent within 4 weeks. According to our definition, treatment was effective in all four patients with a retinal lesion smaller than the optic disc. No systemic side effects of azithromycin were encountered.

Within the first year of follow up, three (27%) patients underwent a recurrent attack of retinitis at follow up months 5, 6, and 7, respectively (Table 1, patients 2, 3, 10). No specific characteristics were noted for the patients who relapsed (specifically, no differences in the size and the location of retinal lesions, in the age of the patients, and their previous response to treatments were observed between the patients with and without relapse). Furthermore, during the follow up period, three patients developed temporary anterior uveitis without an evidence of active chorioretinitis at that time (Table 1, patients 2, 4, 8; all three had fine keratic precipitates scattered across the entire corneal endothelium and elevated intraocular pressure during activity). Anterior uveitis subsided with local symptomatic treatment in all three cases.

### Discussion

The above results show that although azithromycin cannot prevent recurrent disease it may be an effective alternative for patients with ocular toxoplasmosis who cannot tolerate standard therapies.

Azithromycin is a non-toxic antibiotic which penetrates into phagocytic cells and reaches high intracellular and tissue concentrations.<sup>7</sup> In vivo and in vitro efficacy against *T gondii* has been reported, with an effect on the cystic form if administered for longer than 4 weeks.<sup>5</sup> Furthermore, it penetrates readily into brain tissue.<sup>8,9</sup> The concentrations of azithromycin in the ocular tissues are not yet known. Clinical experience with toxoplasmic encephalitis during AIDS has shown beneficial results. However, resistant cases and recurrences have also been reported.<sup>10</sup> We considered azithromycin for the treatment of ocular toxoplasmosis because of its availability and limited toxicity and because it crosses the blood-brain barrier and appears to be widely distributed to brain tissue. The efficacy of drugs which do not cross the blood-brain or blood-retinal barrier in cerebral and severe ocular toxoplasmosis is probably related to the extensive disruption of these barriers. Pyrimethamine, the drug known to be most active against toxoplasmosis, penetrates into cerebral and ocular tissues; however, low concentrations have been measured in cerebrospinal and intraocular fluids (approximately 10% of serum levels).<sup>11-14</sup> The diffusion of trimethoprim, sulphonamides, clindamycin, and atovaquone within the brain or eye is either low or unknown.<sup>8,15-17</sup>

According to clinical experience, the major indications for antitoxoplasmic therapy include retinal lesions in the papillomacular area, large peripheral lesions with a marked inflammatory reaction, and all lesions in immunosuppressed patients.<sup>3</sup> In the immunosuppressed, the clinical manifestations may be extremely severe and, if left untreated, invariably progress.<sup>18,19</sup> Resolution of disease activity in AIDS has been seen following treatment with conventional antiparasitic drugs; however, adverse effects are frequently reported.<sup>20-25</sup> The toxicity of traditional therapies for toxoplasmosis led to discontinuation of treatment in 40% of immunocompromised and 26% of immunocompetent

patients.<sup>2 23 26</sup> The identification of new curative or prophylactic drugs with low toxicity is extremely important not only for immunocompetent patients with ocular disease but also for those with CNS and systemic toxoplasmosis. Azithromycin, given for protection against disseminated *M avium* complex infection, was well tolerated in AIDS patients, even in those with the advanced stage of HIV disease.<sup>27</sup>

It is difficult to evaluate the efficacy of single agent chemotherapy with azithromycin for the selected group of patients suffering from an essentially self limiting disease. In the present study, seven of 11 patients (including four with small lesions) exhibited prompt resolution of the retinal lesions and no side effects of azithromycin. However, the median time to resolution of toxoplasmic retinal lesions is about 8 weeks, irrespective of the therapy given, and smaller lesions have been reported to resolve more quickly.<sup>2</sup> In this selected series the mean time from onset of symptoms to resolution was 7 weeks for the patients classified as a therapeutic successes compared with 10 weeks for the remaining patients. The more rapid resolution among the "therapeutic successes" may have been related to the therapeutic intervention rather than simply time, but the small number of patients studied precludes a definitive conclusion.

Compared with other antiparasitic drugs (pyrimethamine, clindamycin, sulphadiazine) atovaquone and azithromycin had a superior effect against cysts and bradyzoites in vitro.<sup>5</sup> Our hope that azithromycin would be able to control recurrent disease has diminished since we found that three of 11 patients exhibited recurrence within 1 year of follow up. This percentage is similar to that reported for patients receiving standard therapies or no therapy at all.<sup>2</sup> However, all of our patients already had manifest recurrent disease before treatment with azithromycin was initiated. Moreover, our observation that azithromycin does not prevent recurrences only applies for the dosages used in this trial.

A conclusive study on the efficacy of azithromycin would require subdivision of a series of patients according to clinical features as well as evaluation of azithromycin as sole therapeutic agent and as part of multiple regimens (possible synergism with other antiparasitic drugs). Our study indicates that evaluation of the efficacy of azithromycin, preferably by means of randomised studies, is needed to determine its future role in treatment and the possibility of preventing recurrence of ocular toxoplasmosis.

Part of this study was presented (orally) at IV annual meeting of European Research Network on Congenital Toxoplasmosis in Toulouse, France, June 1997.

- 1 Engstrom RE, Holland GN, Nussenblatt RB, et al. Current practices in the management of ocular toxoplasmosis. *Am J Ophthalmol* 1991;111:601-10.
- 2 Rothova A, Meenken C, Buitenhuis HJ, et al. Therapy for ocular toxoplasmosis. *Am J Ophthalmol* 1993;115:517-23.
- 3 Nussenblatt RB, Whitcup SM, Palestine AG. Ocular toxoplasmosis. In: *Uveitis. Fundamentals and clinical practice*. St Louis: Mosby Year Book, 1996:211-28.
- 4 Acers TE. Toxoplasmic retinochoroiditis: a double blind therapeutic study. *Arch Ophthalmol* 1964;71:58-62.
- 5 Huskinson-Mark J, Araujo FG, Remington JS. Evaluation of the effect of drugs on the cyst form of *Toxoplasma gondii*. *J Infect Dis* 1991;164:170-7.
- 6 Boer JH de, Verhagen C, Bruinenberg M, et al. Serologic and polymerase chain reaction analysis of intraocular fluids in the diagnosis of infectious uveitis. *Am J Ophthalmol* 1996;121:650-8.
- 7 Hoepelman IM, Schneider MME. Azithromycin: the first of the tissue-selective azalides. *Int J Antimicrob Agents* 1995;5:145-67.
- 8 Spencer CM, Goa KL. Atovaquone. A review of its pharmacological properties and therapeutic efficacy in opportunistic infections. *Drugs* 1995;50:176-96.
- 9 Jaruratanasirikul S, Hortiwakul R, Tantissarasart T, et al. Distribution of azithromycin into brain tissue, cerebrospinal fluid, and aqueous humor of the eye. *Antimicrob Agents Chemother* 1996;40:825-6.
- 10 Dunne MW, Williams DJ, Young LS. Azithromycin and the treatment of opportunistic infections. *Rev Contemp Pharmacother* 1994;5:373-81.
- 11 Lepout C, Meulemans A, Robine D, et al. Levels of pyrimethamine in serum and penetration into brain tissue in humans. *AIDS* 1992;6:1040-1.
- 12 Weiss LM, Harris C, Berger M, et al. Pyrimethamine concentrations in serum and cerebrospinal fluid during treatment of acute toxoplasma encephalitis in patients with AIDS. *J Infect Dis* 1988;157:580-3.
- 13 McLeod R, Mack D, Foss R, et al and the Toxoplasmosis Study Group. Levels of pyrimethamine in sera and cerebrospinal and ventricular fluids from infants treated for congenital toxoplasmosis. *Antimicrob Agents Chemother* 1992;36:1040-8.
- 14 Kaufman HE. The penetration of daraprim (pyrimethamine) into monkey eye. *Am J Ophthalmol* 1961;52:402-4.
- 15 Norby R. A review of the penetration of antibiotics into CSF and its clinical significance. *Scand J Infect Dis* 1978;14:296-309.
- 16 Keusch GT, Present DH. Summary of a workshop on clindamycin colitis. *J Infect Dis* 1976;133:578-87.
- 17 Reeves DS, Wilkinson PJ. The pharmacokinetics of trimethoprim and trimethoprim/sulphonamide combinations, including penetration into body tissues. *Infection* 1979;7 (suppl 4):330-41.
- 18 Holland GN, Engstrom RE, Glasgow BJ, et al. Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1988;106:653-67.
- 19 Richards FO Jr, Kovacs JA, Luft BJ. Preventing toxoplasmic encephalitis in persons infected with human immunodeficiency virus. *Clin Infect Dis* 1995;21:49-56.
- 20 Lepout C, Chene G, Morlat P, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. *J Infect Dis* 1996;173:91-7.
- 21 Cochereau-Massin I, LeHoang P, Lautier-Frau M, et al. Ocular toxoplasmosis in human immunodeficiency virus-infected patients. *Am J Ophthalmol* 1992;114:130-5.
- 22 Aarons E, Hawkins D, Nelson N, et al. Testing and management of *Toxoplasma* serology in HIV-positive patients. *AIDS* 1996;10:443-4.
- 23 Katlama C, De Wit S, O'Doherty E, et al and the European Network for treatment of AIDS (ENTA). Toxoplasmosis study group. *Clin Infect Dis* 1996;22:268-75.
- 24 Peacock JE Jr, Greven CM, Cruz JM, et al. Reactivation of toxoplasmic retinochoroiditis in patients undergoing bone marrow transplantation: is there a need for chemoprophylaxis? *Bone Marrow Transplant* 1995;15:983-7.
- 25 Jacobson MA, Besch CL, Child C, et al. Primary prophylaxis with pyrimethamine for toxoplasmic encephalitis in patients with advanced human immunodeficiency virus disease: results of a randomized trial. *J Infect Dis* 1994;169:384-94.
- 26 Luft BJ, Hafner R, Korzun AH, et al. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1993;329:995-1000.
- 27 Havlir DV, Dubé MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. *N Engl J Med* 1996;335:392-8.