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 folinic 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. 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 folinic 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. 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). 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 folinic 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...
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Table 1 Azithromycin for ocular toxoplasmosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Indication for treatment</th>
<th>Information between onset and azithromycin medication (weeks)</th>
<th>Size of retinal lesion (DD)</th>
<th>Duration of retinitis (weeks)</th>
<th>Complications</th>
<th>Visual acuity</th>
<th>Follow up (months)</th>
<th>Retinitis recurrence (follis up, months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1, M, 25</td>
<td>patient’s choice</td>
<td>&lt;1</td>
<td>1</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>20/50</td>
<td>20/20</td>
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<tr>
<td>2, M, 44</td>
<td>patient’s choice</td>
<td>2</td>
<td>2.5</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>20/60</td>
<td>20/20</td>
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<tr>
<td>3, F, 24</td>
<td>patient’s choice</td>
<td>&lt;1</td>
<td>1</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>20/30</td>
<td>20/25</td>
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<tr>
<td>4, M, 43</td>
<td>patient’s choice</td>
<td>&lt;1</td>
<td>3</td>
<td>8</td>
<td>—</td>
<td>—</td>
<td>20/60</td>
<td>20/20</td>
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<tr>
<td>5, F, 33</td>
<td>patient’s choice</td>
<td>&lt;1</td>
<td>1</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>20/30</td>
<td>20/20</td>
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<tr>
<td>6, M, 28</td>
<td>intolerant to triple</td>
<td>5</td>
<td>1.5</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>20/60</td>
<td>20/25</td>
</tr>
<tr>
<td>7, F, 31</td>
<td>with triple treatment*</td>
<td>&gt;8</td>
<td>6</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>20/60</td>
<td>20/20</td>
</tr>
<tr>
<td>8, F, 29</td>
<td>with triple treatment*</td>
<td>&gt;8</td>
<td>4</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>20/60</td>
<td>20/20</td>
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<tr>
<td>9, M, 54</td>
<td>progressive disease</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>20/60</td>
<td>20/25</td>
</tr>
<tr>
<td>10, F, 73</td>
<td>intolerant to triple</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>20/60</td>
<td>20/20</td>
</tr>
<tr>
<td>11, F, 60</td>
<td>intolerant to triple</td>
<td>2</td>
<td>1.5</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>20/60</td>
<td>20/20</td>
</tr>
</tbody>
</table>

*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).

Azithromycin is a non-toxic antibiotic which penetrates into phagocytic cells and reaches high intracellular and tissue concentrations.7 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.5 Furthermore, it penetrates readily into brain tissue.6 7 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.8 9 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).11 12 The diffusion of trimethoprim, sulphamides, clindamycin, and atovaquone within the brain or eye is either low or unknown.13–15

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.7 In the immunosuppressed, the clinical manifestations may be extremely severe and, if left untreated, invariably progress.16 17 Resolution of disease activity in AIDS has been seen following treatment with conventional antiparasitic drugs; however, adverse effects are frequently reported.18 19 The toxicity of traditional therapies for toxoplasmosis led to discontinuation of treatment in 40% of immunocompromised and 26% of immunocompetent...
patients.\textsuperscript{2, 13-28} 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 \textit{M avium} complex infection, was well tolerated in AIDS patients, even in those with the advanced stage of HIV disease.\textsuperscript{27}

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.\textsuperscript{7} 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, sulphanidaizine) atovaquone and azithromycin had a superior effect against cysts and bradyzoites in vitro.\textsuperscript{5} 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.\textsuperscript{2} 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.

\begin{itemize}
\item \textsuperscript{10} Dunne MW, Williams DJ, Young LS. Azithromycin and the treatment of opportunistic infections. \textit{Res Concep Pharmacother} 1994;5:373–81.
\item \textsuperscript{14} Kaulman HE. The penetration of daraprim (pyrimethamine) into monkey eye. \textit{Am J Ophthalmol} 1961;52:402–4.
\item \textsuperscript{15} Norby R. A review of the penetration of antibiotics into the CNS. \textit{Am J Ophthalmol} 1978;84:317–25.
\item \textsuperscript{16} Keusch GT, Present DH. Summary of a workshop on clindamycin colitis. \textit{J Infect Dis} 1976;133:578–87.
\item \textsuperscript{17} Reeves DS, Watanuki P. The pharmacokinetics of trimethoprim and trimethoprin/sulphonamide combinations, including penetration into body tissues. \textit{Infection} 1979;7(suppl 4):370–41.
\item \textsuperscript{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? \textit{Bone Marrow Transplant} 1995;15:983–7.
\end{itemize}
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