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.

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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 approach is to stop retinal damage by hampering multiplication of the parasites during the active stage of retinitis. 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. 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.

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. 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 toxoplasmic retinitis 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
### Azithromycin for ocular toxoplasmosis

**Table 1 Azithromycin for ocular toxoplasmosis**

<table>
<thead>
<tr>
<th>Patient No, sex, age (years)</th>
<th>Indication for treatment</th>
<th>Interval between onset and azithromycin medication (weeks)</th>
<th>Size of retinal lesion (DD)</th>
<th>Duration of retinitis (weeks)</th>
<th>Complications Systemic Ocular</th>
<th>Visual acuity Onset</th>
<th>Additional treatment</th>
<th>Follow up (months)</th>
<th>Retinitis recurrence (follow up, months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, M, 25</td>
<td>patient's choice</td>
<td>&lt;1</td>
<td>1</td>
<td>3</td>
<td>—</td>
<td>pyrimethamine and prednisone</td>
<td>20/50</td>
<td>20/20</td>
<td>21</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>pyrimethamine and prednisone</td>
<td>20/60</td>
<td>20/20</td>
<td>20</td>
</tr>
<tr>
<td>3, F, 24</td>
<td>patient's choice</td>
<td>&lt;1</td>
<td>1</td>
<td>4</td>
<td>—</td>
<td>pyrimethamine and prednisone</td>
<td>20/30</td>
<td>20/25</td>
<td>22</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>pyrimethamine and sulfadiazine</td>
<td>20/60</td>
<td>20/20</td>
<td>20</td>
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<td>5, F, 33</td>
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<td>&lt;1</td>
<td>1</td>
<td>3</td>
<td>—</td>
<td>prednisone</td>
<td>20/30</td>
<td>20/20</td>
<td>20</td>
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<td>6, M, 28</td>
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<td>5</td>
<td>1.5</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>20/200</td>
<td>20/25</td>
<td>21</td>
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<tr>
<td>7, F, 31</td>
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<td>&gt;8</td>
<td>6</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>8, F, 29</td>
<td>progressive disease</td>
<td>&gt;8</td>
<td>4</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>CF</td>
<td>20/200</td>
<td>21</td>
</tr>
<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>
<td>23</td>
</tr>
<tr>
<td>10, F, 73</td>
<td>tolerant to triple</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>HM</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>11, F, 69</td>
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<td>4</td>
<td>—</td>
<td>—</td>
<td>CF</td>
<td>20/50</td>
<td>13</td>
</tr>
</tbody>
</table>

*Triple treatment included pyrimethamine, sulfadiazine, 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.\(^3\)\(^9\) 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.\(^10\)

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).\(^11\)\(^14\) The diffusion of trimethoprim, sulphonamides, clindamycin, and atovaquone within the brain or eye is either low or unknown.\(^15\)\(^17\)

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.\(^10\)\(^15\)

Resolution of disease activity in AIDS has been seen following treatment with conventional antiparasitic drugs; however, adverse effects are frequently reported.\(^20\)\(^25\) The toxicity of traditional therapies for toxoplasmosis led to discontinuation of treatment in 40% of immunocompromised and 26% of immunocompetent

### 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.

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1. Azithromycin is a non-toxic antibiotic which penetrates into phagocytic cells and reaches high intracellular and tissue concentrations. \(^7\)
2. 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. \(^5\)
3. Furthermore, it penetrates readily into brain tissue. \(^3\) \(^9\)
4. 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. \(^10\)
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7. 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. \(^7\)
8. In the immunosuppressed, the clinical manifestations may be extremely severe and, if left untreated, invariably progress. \(^10\) \(^15\)
9. Resolution of disease activity in AIDS has been seen following treatment with conventional antiparasitic drugs; however, adverse effects are frequently reported. \(^20\) \(^25\) The toxicity of traditional therapies for toxoplasmosis led to discontinuation of treatment in 40% of immunocompromised and 26% of immunocompetent
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. 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, sulfadiazine) atovaquone and azithromycin had a superior effect against cysts and bradyzoites in vitro. Atovaquone and azithromycin had a superior effect against cysts and bradyzoites in vitro. Recent studies have shown that azithromycin is an effective drug for the treatment of toxoplasmic retinochoroiditis in patients with acquired immunodeficiency syndrome. The authors concluded that azithromycin may be an effective drug for the treatment of toxoplasmic retinochoroiditis in patients with acquired immunodeficiency syndrome.

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