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DISEASE OF THE YEAR/REVIEW

Therapy for Ocular Toxoplasmosis

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ABSTRACT

Purpose: To review current evidence for the treatment of ocular toxoplasmosis (OT).

Design: Narrative review and expert recommendations.

Methods: Meta-analysis and selected original articles from the medical literature were reviewed critically. Expert recommendations were analyzed.

Results: Numerous observational studies suggest a benefit of short-term antimicrobial therapy for toxoplasmic retinochoroiditis in immunocompetent patients, although its efficacy has not been proven in randomized clinical trials. A randomized clinical trial revealed that intermittent trimethoprim/sulfamethoxazole treatment could decrease the rate of recurrence in high-risk patients. Intravitreal injection of clindamycin and dexamethasone was an acceptable alternative to the classic treatment for OT in a randomized clinical trial.

Conclusions: Opinions about therapy differ and controversy remains about its type, efficacy, and length. Intravitreal therapy may be promising for OT. A recent description of the presence of parasitemia in patients with active and inactive ocular toxoplasmosis raises new questions that need to be explored.

Keywords: antibiotics, ocular toxoplasmosis, recurrences, steroids, therapy, treatment, uveitis

INTRODUCTION

Toxoplasma gondii, an opportunistic parasite, is responsible for 30–50% of posterior uveitis cases in immunocompetent individuals, and in some countries is one of the most important causes of visual impairment.[1,2] Treatment for ocular toxoplasmosis is a matter of controversy. A written questionnaire distributed to all physician-members ($n = 147$) of the American Uveitis Society found that 9 separate drugs were used in a possible 24 different regimes.[3] A survey conducted among 1000 U.S.-based ophthalmologists found wide variations in practice with respect to the use of corticosteroids in addition to anti-parasitic therapy to treat ocular toxoplasmosis.[4]

Two Cochrane reviews have been established for ocular toxoplasmosis.[5,6] The first review, begun in 2002 and updated in 2009, examined whether antibiotics are effective in the treatment of toxoplasmic retinochoroiditis.[5] A recent further Cochrane review, started in 2008, will assess the evidence for the effect of steroids administered locally versus steroids administered systemically with or without antibiotics.[6] The Cochrane reviews were justified because there is controversy about the use of antibiotics in peripheral lesions.[5] Also, the natural history of ocular toxoplasmosis in patients without treatment is variable, thus some patients can recover in a few weeks without antibiotics.[5] Arguments for antibiotic use are that antibiotics can reduce the number of recurrences and that they could help to speed inflammation resolution.[7] The Cochrane review found only three studies[8–10] that compared antibiotics to no treatment or to a placebo; it was concluded that no strong evidence exists that antibiotics (short or long term) prevent vision loss, alter the speed of resolution, or have any effect on the recurrence rate.[5]

An additional issue emerged recently when comparative clinical series were analyzed between

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continents. A comparative prospective cohort study of congenitally infected children in Brazil and Europe found that Brazilian children had eye lesions that were larger, more numerous, and more likely to affect the part of the retina responsible for central vision, when compared with their European counterparts.[11] Additionally, parasite genotyping indicates that a different parasite strain is responsible for disease in Europe than in South America.[12] Differences between strains may be an explanation for the high incidence and rate of complications in South American children compared with those in Europe.[11] Previous comparative data found significant differences in immunological response between South American and European patients with ocular toxoplasmosis.[13] These results support the notion that South American patients should be given different treatment than that specified in standard European protocols.[14]

An excellent review appeared recently[15] as part of a commemorative issue of the journal *Memorias do Instituto Oswaldo Cruz* for the centennial of the discovery of *Toxoplasma*. The Cochrane reviews and the centennial review analyzed and discussed the results of available studies but they did not recommend practical options and regimes. Therefore, we will limit our review to present practical therapeutic options in different situations based on the best of the available evidence and will update this information with recently published results of comparative trials for different antibiotic regimes.

METHODS

Keywords (ocular toxoplasmosis, therapy, treatment, trial) were selected in a review of the literature through Pubmed (www.nlm.nih.gov/) from 2008 to May 2011. We summarized the results of the study and the type and size of the sample and qualify the level of evidence.

RESULTS

Pubmed Search 2008–2011 and Updated Analysis of Bibliography for Therapy of Ocular Toxoplasmosis

The term "ocular toxoplasmosis and therapy" resulted in 44 documents, "ocular toxoplasmosis and treatment" gave 60 results, and "ocular toxoplasmosis and trials" 3 results. No language restriction was considered. After checking the abstracts obtained with the terms ocular toxoplasmosis and treatment, all comparative trials or observational studies regarding treatment for ocular toxoplasmosis were also included in the results with the other terms. After analysis of selected complete articles, we found that only 1 study[16] was a prospective, randomized, single-masked clinical trial. It consisted of 68 Iranian patients with active ocular toxoplasmosis assigned randomly to 2 treatment groups: 34 in an intravitreal clindamycin plus dexamethasone group and 34 in the classic treatment group (oral pyrimethamine plus sulfadiazine). The other 3 studies were retrospective. One of these studies was a noncomparative, retrospective, multicenter, interventional case series of 12 eyes of 12 consecutive Venezuelan patients with posterior pole (zone 1) lesions who were treated weekly (or every 4 weeks during pregnancy) with intravitreal injections of clindamycin (1.5 mg/0.1 mL) and dexamethasone (400 μg/0.1 mL).[17] A second retrospective study was a nonrandomized clinical trial in German patients.[18] Forty-one immunocompetent patients were treated for *Toxoplasma* retinochoroiditis with atovaquone between 1999 and 2006. The diagnosis was based on clinical signs alone. Atovaquone was given 750 mg 2–3 times daily together with oral steroids. The third study was a retrospective analysis of 19 ocular toxoplasmosis patients treated with trimethoprim/sulfamethoxazole and azithromycin with or without corticosteroid.[19]

The analysis of the results indicates that these studies did not add additional evidence for the meta-analysis (by adding randomized controlled trials comparing antibiotics versus not antibiotics) aiming to resolve whether antibiotics are or are not necessary in the therapy of ocular toxoplasmosis. However, two of them, one prospective randomized[16] and other observational retrospective,[17] support the proposition that intravitreal injection of clindamycin and dexamethasone could be as effective as classical treatment with oral antibiotics and without significant adverse events.

Basis for Expert's Recommendations for Different Clinical Situations in Ocular Toxoplasmosis

Treatment in Infants with Congenital Infection

Early prenatal treatment is important to reduce the risk of retinochoroiditis in congenitally infected children. In two different studies of congenitally infected infants, a delay of more than 8 weeks between maternal seroconversion and treatment onset was associated with an increased risk of retinochoroiditis during the first 2 years of life.[20,21] Regarding postnatal treatment, opinions diverge because of conflicting results from observational studies. In a prospective European cohort, prenatal treatment did not significantly reduce the risk of retinochoroiditis.[22] In contrast, in a prospective study, a cohort of congenitally infected referred children who were not treated during the first year of life had an eye lesion rate that was higher compared to historical records from children who were treated.[23] These conflicting results can explain why postnatal treatment opinions diverge considerably in terms of medicines, schedules, and duration of treatment. Congenital toxoplasmosis produces a chronic ophthalmological disease and it has been reported that 10-year follow-up is necessary for a precise evaluation of the retinal lesions occurrence.[24]

A recently emerging issue is that *Toxoplasma* congenital infection in South America should be considered different than that in Europe. In a comparative prospective study in children with congenital toxoplasmosis diagnosed at birth by universal screening in Europe and Brazil and followed up until the age of 4, Brazilian children, when compared to European children, had a 5 times higher risk of developing eye lesions, and their lesions were larger, more numerous, and more likely to affect the part of the area of the retina responsible for central vision.[11] Two-thirds of Brazilian children infected with congenital toxoplasmosis had eye lesions by 4 years of age compared with 1 in 6 European children.[11] These stark differences are likely due to the predominance of more virulent parasite genotypes in Brazil, which are rarely found in Europe.[12]

Further research is required to determine whether virulence factors are associated with prolongation of the tachyzoite phase, which could create a longer therapeutic window for effective treatment before tissue cyst formation.[25] Randomized controlled trials are needed most urgently in South America to determine the effectiveness of postnatal treatment for congenital toxoplasmosis and, hence, whether neonatal screening is worthwhile. Extrapolation of results on treatment effectiveness across continents may not be justified if pharmacological effects differ according to parasite genotype.[14] Delay in diagnosis and treatment may worsen the outcome and this is more significant in children, when frequently the vision is lost as a consequence of the retinochoroiditis or retinal complications.[22,23]

Ocular Toxoplasmosis during Pregnancy

During pregnancy, active recurrent lesions usually do not represent a risk to the fetus. In the literature there are 3 case reports of congenital toxoplasmosis in mothers with old retinochoroideal lesions.[26] The mother should be treated as indicated, keeping in mind the teratogenic potential of the antimicrobial agents such as pyrimethamine and the sulfonamides, especially during the early stages of pregnancy.[27] Combined intravitreal injection of clindamycin and dexamethasone could be another treatment option for such cases.[16]

Treatment of Active Toxoplasmic Retinochoroiditis in Adults

Healed lesions should not be treated. As ocular toxoplasmosis is a self-limiting disease, some clinicians will not treat small peripheral lesions. In adults, despite being a self-limiting disease in most instances, OT may cause decreased visual acuity secondary to optic nerve or macular involvement and severe vitritis.[3,15] The aim of treatment is to arrest parasite multiplication during the active period of retinochoroiditis and to minimize damage to the retina and optic disc.[3,15] Since active lesions, may be associated with loss of visual acuity due to intense vitritis, macular traction, or detachment, treating any active lesions may be indicated.[3,15] Moreover, tachyzoites released from reactivated tissue cysts could spread to other sites in the retina. For this reason, some believe that treatment of any active lesion may be associated with a decreased overall tachyzoite load, consequently diminishing the risk of recurrences.[3]

Active lesions, especially those that are vision threatening due to their retinal localization, are regularly treated with a combination of dihydrofolate inhibitors, sulfonamides, and steroids. An evidence-based systematic review investigated the effectiveness of systemic antibiotic treatment. Only three studies were randomized controlled trials[8–10] and none gave clear evidence to support routine antibiotic treatment of acute ocular toxoplasmosis.[5] None of these clinical trials confirmed that short-term drug therapy was effective for treatment of active toxoplasmic retinochoroiditis.[5] However, the review should not be interpreted to mean that treatment has no effect.[5] Although current short-term treatments do not prevent recurrent disease, and it has been difficult to demonstrate that treatment alters the natural history of active disease, there has been observational evidence of treatment effects in some patients. For example, in a nonrandomized study,[28] there was a relationship between pyrimethamine/sulfadiazine treatment and reduction of lesion size, determined by comparing the size of active retinal inflammatory lesions to the size of resulting inactive retinochoroidal scars.[28] However, it should be kept in mind that the effect on size was very small and treatment itself produced adverse effects.[28] Thus, the practical benefit of this observed treatment effect remains to be determined.[5] Other potential benefits of treatment, such as a reduction in the disease duration, could not be demonstrated. Nevertheless, based on their experience, most uveitis specialists agree that treatment of toxoplasmic retinochoroiditis is reasonable, although there is no consensus regarding the best treatment regimens.[3] One argument is that antibiotics can reduce recurrences; in support of this belief, a study of recurrences in Colombian patients found a significantly greater adjusted recurrence index in the group treated with systemic steroids alone.[29]

There is a large discrepancy between the lack of benefit that can be demonstrated in humans and evidence from animal studies that antimicrobial drugs are highly effective for treatment of active toxoplasmosis. This efficacy is typically reported in terms of reduced animal mortality.[30] Although a treatment effect has been difficult to confirm for immunocompetent patients, there are certain situations when anti-*T. gondii* drug treatment appears to have remarkable effects in humans. For instance, chronic active toxoplasmic retinochoroiditis in patients with AIDS will rapidly become inactive with treatment.[31–34]

While some antimicrobial agents, such as atovaquone and azithromycin, reduce the number of tissue cysts in animal models,[35] recurrences have not been prevented with short-term therapy using either atovaquone[36,37] or azithromycin[38] in humans, although fewer recurrences

were found by using atovaquone in small lesions.[37] It has been hypothesized that a lack of treatment effect in patients whose retinal lesions are characterized by thickened granulomata could be related to failure of drug to penetrate the lesions and reach parasites.[15] However, it should be kept in mind that the only drugs available clinically to treat toxoplasma are active against tachyzoites not bradyzoites.[15] The success of antibiotics in immunosuppressed patients is likely because the retinal infection is due to retinal tachyzoite invasion uninhibited by an immune response. Thus, the tachyzoite organisms will not likely be stimulated to convert to bradyzoites.[15]

New data can change our understanding about how antibiotics can act during noninflammatory stages. For example, a recent report demonstrated that there is *Toxoplasma* parasitemia in Brazilian patients with active or inactive ocular toxoplasmosis.[39] This raises the question whether a similar phenomenon might be present in European patients. If so, this would support the need for antibiotic prophylaxis during recurrence-free periods to control the eventual egress of tachyzoites, thereby reducing the probability they reach the retina and induce new lesions. Clearly, further work is required to evaluate this possibility.

Factors That Influence Extrapolation of Therapeutic Decisions from Clinical Trials and That Require a Better Understanding of Disease

Clinical trials that target specific populations or patients having lesions with specific characteristics are more successful at demonstrating treatment effects. For this reason it is important to understand the relationship between the infecting parasite and the nature of the resulting disease to justify therapeutic decisions that could be extrapolated to other clinical situations. For instance, if the infecting parasite type could be identified easily on the basis of a serological test, and it is confirmed that certain parasite types are associated with a substantially increased risk of severe ocular disease, decisions to use potentially toxic drugs could be made in a more rational manner. Furthermore, the role of corticosteroids in the management of ocular toxoplasmosis needs to be evaluated more precisely; specifically, the contribution of inflammation to tissue destruction in various situations needs to be clarified. Histopathologic studies of eyes from immunocompromised patients with toxoplasmic retinochoroiditis show a lack of inflammatory cells in infected retina[31] and corticosteroid therapy has not been necessary to control toxoplasmic retinochoroiditis in such patients.[31] Vision loss can first occur with lesion reactivation, indicating the necessity to develop strategies for the prevention of recurrences.[3] For example, one study showed a statistically significant reduction in recurrence rates among patients in southern Brazil given intermittent trimethoprim/sulfamethoxazole over a 20-month period.[7] To apply this strategy of secondary prophylaxis properly, it will be necessary to identify those patients at greatest risk of recurrence and to get a better understanding of the interval during which recurrences are most likely to occur. With this approach, the patients who may not benefit from treatment will not be exposed unnecessarily to the toxic effects of antimicrobial drugs.

Corticosteroid therapy without the concomitant use of antimicrobial agents, even in immunocompetent patients, can lead to severe tissue destruction.[40] The use of systemic steroids without antibiotics and subconjunctival injection of steroids were identified as the main factors related to recurrence in a group of patients.[29] Fulminant toxoplasma retinochoroiditis has also been observed in patients treated with intravitreal steroids alone.[41] These observations suggest that parasite proliferation, rather than inflammation, is the main cause of tissue injury in these cases. However, despite the potential unfavorable effects of corticosteroids, many uveitis specialists have seen patients who were initially treated with corticosteroids alone and did well.[3] It is likely that there are substantial qualitative differences in the inflammatory responses that occur among various groups of patients.[31] Also, different parasite types may elicit unique immune responses with different consequences to host tissue. An understanding of these differences may ultimately allow an individualized approach to the use of corticosteroids in the management of ocular toxoplasmosis.[6]

Recommended Therapeutic Regimens

Classic Therapy

The most frequent treatment for ocular toxoplasmosis ("classic therapy") consists of pyrimethamine and sulfadiazine plus corticosteroids. In this therapy,[8] an initial dose of 75–100 mg of pyrimethamine is given daily for 2 days followed by a 25- to 50-mg dose daily. Sulfadiazine, 2–4 g, is given daily for 2 days, followed by a 500-mg to 1-g dose every 6 h as well as 5 mg of folinic acid daily for 4–6 weeks (Table 1). Oral prednisolone (1 mg/kg daily) is given from the third day of

TABLE 1 Experts consensus recommended regime for ocular toxoplasmosis: first line recommended oral antibiotics.

Drug	Adult dose	Pediatric dose
Pyrimethamine	200 mg oral first day follow by 75 mg once a day	2 mg/kg first dose and then 1 mg/kg day during 1 year (congenital form) or 4–5 weeks in acquired infections
Sulfadiazine	4 g/day	50 mg/kg twice daily (100 mg/kg/day) during 1 year in congenital infection or for 4–5 weeks in acquired forms
Folinic acid	15 mg/day	7.5 mg/ day

therapy and tapered over 2–6 weeks.[3] Good response with resolution of inflammation and apparition of the characteristic hyperpigmentation of lesion can be observed after 4–6 weeks of treatment (Figure 1).

Classic treatment may have risks that depend on patient susceptibility to drug toxicity or allergic reactions.[42] When pyrimethamine is administered weekly, blood cell and platelet count monitoring is recommended.[42] Folinic acid should be also administered to protect against leukopenia and thrombocytopenia.[42] Likewise, sulfadiazine may cause a severe allergic reaction, which can be life-threatening in some patients.[42]

Alternative Antibiotics

Trimethoprim (80 mg)/sulfamethoxazole (400 mg) every 12 h plus oral prednisone (1 mg/kg started after 3 days) is an alternative treatment option. This regime was shown recently to have similar efficacy to classic therapy in a randomized clinical trial.[43] Other alternative treatment regimens include quadruple drug therapy (classic regimen plus clindamycin, 300 mg for times a day), clindamycin alone, or combined with trimethoprim/sulfamethoxazole, spiramycine, minocycline, azithromycin, atovaquone, and clarithromycin.[3,15] Additionally, the cost of these drugs is high and they are not readily available in some areas. Also, these drugs are not safe to use in pregnant women, and there is no liquid formula of such drugs for pediatric patients, although atovaquane is available in United States in liquid suspension. Compliance can also be difficult, considering that patients need to receive up to 10 pills per day. Nonmedical treatment such as laser photocoagulation or cryotherapy has been reported by a few clinicians in one survey in the United States[3] and lesions were thought to have come under better control after the procedure, although the basis for this assessment was not stated.[3]

Intravitreal Therapy

Intravitreal clindamycin injection and dexamethasone to treat toxoplasmosis retinochoroiditis is a promising approach.[16,43] Intravitreal drug administration bypasses ocular barriers and thereby delivers a high drug concentration directly to intraocular tissues, avoiding systemic exposure and its risk of complications. Intravitreal therapy could be more convenient, has a better safety profile, produces greater drug availability, and results in fewer follow-up visits and hematologic evaluations.[16,43] In a recent study, the mean number of injections was 1.6 (range 1–3) given every 2 weeks.[16] Weekly injections of the same drugs have also been suggested.[44] Having a good intracellular penetration, clindamycin penetrates cells well and provides a high intracellular concentration against T. gondii.[45] It can reach an intracellular/extracellular ratio of 43 compared to other antibiotics, such as erythromycin and levofloxacin, which have ratios of 14 and 6, respectively.[45] Clindamycin,1.5 mg, given intravitreally was nontoxic to the retina and had a half-life of 5.6 days. Following 1-mg intravitreal clindamycin injection, its concentration remained ≥1.6 μg/mL for about 40 h, which is higher than the 50% inhibitory concentration for T. gondii.[16,45] Newly acquired toxoplasmosis in IgM-positive patients may be better treated with systemic therapy, a point supported by the fact that lesion

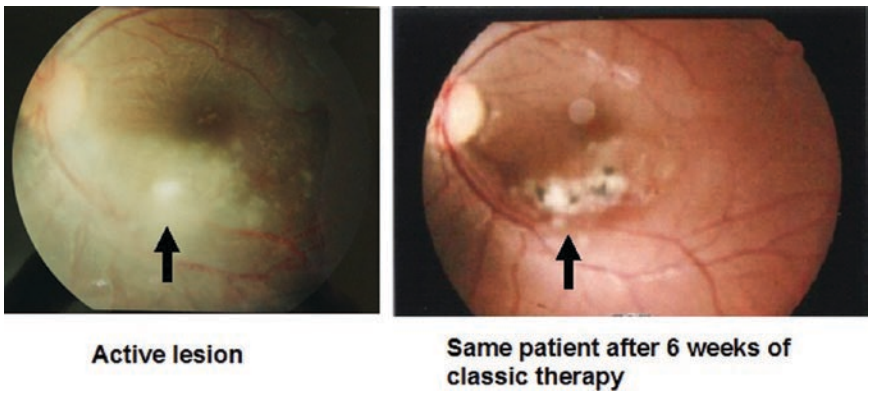

FIGURE 1 Eye fundoscopy of active primary *Toxoplasma* retinochoroiditis lesion treated with classic therapy (pyrimethamine–sulfadoxine plus oral prednisolone during 4 weeks) and resolution of the inflammation after 6 weeks of treatment.

TABLE 2 Second line antibiotics.

Drugs	Adult dose	Pediatric dose
Trimethoprim (TMP)-sulfametoxazol (SMX)	TMP (160 mg)/SMX (800 mg) every 12 h or 2 pills TMP (80 mg)/SMX (400 mg) every 12 h for 6 weeks	No reports for use in children with congenital forms
Azithromycin	500 mg/day for 5 weeks	10 mg/kg/day during 2 months
Intravitreal clindamycin plus dexamethasone	One injection 1 mg intravitreal clindamycin and 400 μg dexamethasone	Not reported

size reduction has been noted to be greater following classic vs. intravitreal therapy.[16] Another intravitreal medication is dexamethasone, which has been used in the management of endophthalmitis[46] and as an adjunct treatment for ocular toxoplasmosis.[16]

Treatment in Immunocompromised Patients

In immunocompromised patients, the treatment regimen is partially modified. It should be emphasized that any active retinal lesion in immunocompromised patients demands treatment because the risk is high of infection dissemination and related complications. Pyrimethamine has an antagonistic activity against zidovudine, an antiretroviral agent used in the treatment of AIDS.[34] For this reason, and because of the risk of drug-induced bone marrow suppression, pyrimethamine should be avoided or used in lower dosage in the treatment regimen of patients with HIV/AIDS who receive highly active antiretroviral therapy (HAART). Lifetime maintenance therapy including either a lower dosage of pyrimethamine combined with sulfadiazine or clindamycin or trimethoprim/sulfamethoxazole is crucial to prevent relapse and dissemination of the infection.[34] Atovaquane is an alternative in these patients.[36] In HIV-infected adult patients receiving effective highly active antiretroviral therapy, primary and secondary prophylaxis against toxoplasmic encephalitis can be safely discontinued after the $CD4^+$ T-cell count has increased to □200 cells/mm^3 for more than 3 months.[47]

CONCLUSIONS

Opinions about therapy differ and controversy remains about its type, efficacy, and length. Intravitreal therapy may be promising for ocular toxoplasmosis. A better clinical and physiopathological understanding can lead to more effective strategies to prevent and treat this common cause of visual impairment.

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