Interventions for Toxoplasma Retinochoroiditis

A Report by the American Academy of Ophthalmology

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Objective: To evaluate the available evidence in peer-reviewed publications about the outcomes and safety of interventions for toxoplasma retinochoroiditis (TRC).

Methods: Literature searches of the PubMed and the Cochrane Library databases were conducted last on July 20, 2011, with no date restrictions. The searches retrieved 275 unique citations, and 36 articles of possible clinical relevance were selected for full text review. Of these 36 articles, 11 were deemed sufficiently relevant or of interest, and they were rated according to strength of evidence.

Results: Eight of the 11 studies reviewed were randomized controlled studies, and none of them demonstrated that routine antibiotic or corticosteroid treatment of TRC favorably affects visual outcomes or reduces lesion size. There is level II evidence from 1 study suggesting that long-term treatment with combined trimethoprim and sulfamethoxazole prevented recurrent disease in patients with chronic relapsing TRC. Adverse effects of antibiotic treatment were reported in as many as 25% of patients. There was no evidence supporting the efficacy of other nonmedical treatments such as laser photocoagulation.

Conclusions: There is a lack of level I evidence to support the efficacy of routine antibiotic or corticosteroid treatment for acute TRC in immunocompetent patients. There is level II evidence suggesting that long-term prophylactic treatment may reduce recurrences in chronic relapsing TRC. Adverse effects of certain antibiotic regimens are frequent, and patients require regular monitoring and timely discontinuation of the antibiotic in some cases.

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The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment is to evaluate the outcomes and safety of interventions for toxoplasma retinochoroiditis (TRC).

Background

Toxoplasma gondii is an ubiquitous human parasite that is a leading infectious cause of posterior uveitis worldwide.[1] *T gondii* is an obligate intracellular parasite that affects both humans and animals. Members of the Felidae (cat) family serve as definitive hosts. Serologic evidence of previous toxoplasma infection is present in approximately 16% of persons 12 to 49 years of age in the United States.[2] Toxoplasma retinochoroiditis is a potentially blinding necrotizing retinitis that may have a recurrent course. Acute episodes commonly cause conjunctival injection, photophobia, floaters, and variably decreased vision; they typically resolve in 6 to 8 weeks, leaving a healed retinochoroidal scar. Chronic complications include persistent vitreous opacities, epiretinal membrane, and cystoid macular edema and can result in visual impairment. Permanent vision loss may occur if lesions affect the macula or optic nerve head.

The lifetime risk of TRC ranges considerably in the literature, depending on geographic location. In the United Kingdom, incidence of symptomatic TRC is estimated to occur in 18 of 100 000 natives (95% confidence interval, 11–25), but in as many as 382 of 100 000 people born in West Africa (95% confidence interval, 99–664).[3]

For many years, most cases of ocular toxoplasmosis were thought to be the result of reactivation of congenital infection.[4] This belief was promoted in part by an extensive review published by Perkins in 1973,[5] in which nearly all cases of TRC were believed to be of congenital origin. However, more recent lines of evidence indicate that most

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individuals with ocular toxoplasmosis may be infected with *T gondii* after birth.[6]

Friedmann and Knox[7] described 3 distinct morphologic forms of toxoplasma lesions: large destructive lesions, punctate inner lesions, and punctate outer lesions. Papillitis and neuroretinitis are well-known atypical presentations, and a severe necrotizing form can be seen in immunocompromised hosts. Lesions greater than 1 disc area may persist longer and have a higher rate of complications and vision loss than smaller lesions.[7] There also have been reports demonstrating a positive relationship between lesion size and duration of disease activity.[8] Recent observations suggest that parasite proliferation in addition to inflammation is a major cause of tissue damage,[6] and in a nonrandomized study, Rothova et al[8] found a positive relationship between treatment with combined pyrimethamine and sulfadiazine and a reduction of final lesion size. In addition, animal studies consistently have demonstrated that antimicrobial drugs are highly effective in the treatment of active toxoplasmosis (usually measured as reduced mortality), and chronically active TRC in patients with AIDS has been reported to become rapidly inactive with antibiotic treatment.[6,9]

For these reasons, there is an increasing trend among uveitis specialists to treat patients who have active TRC. However, there is a lack of consensus about the best treatment regimen. A survey published in 2002 revealed a total of 9 antibiotic drugs used in 24 different regimens as the treatment of choice among 79 responding uveitis specialists.[10] There is also controversy about initiation and timing of adjunctive therapy with corticosteroids. Treatment of patients with latent disease also is controversial because none of the currently available antibiotics has been shown to kill bradyzoites (the encysted form of *T gondii* found in tissue cysts) effectively in humans.

Despite the focus of numerous publications and the common practice of treating active lesions, there continues to be underlying uncertainty about the efficacy of treatments for TRC in immunocompetent patients and large variations in practice patterns among clinicians throughout the world. The benefits of treatment also should be weighed against the cost of treatment and the risks of adverse effects of antibiotic and corticosteroid use. For example, sulfa antibiotics can cause life-threatening hypersensitivity reactions such as Stevens-Johnson syndrome.

Description of the Intervention

Interventions for TRC aim to reduce temporary or permanent vision loss by limiting the severity and duration of inflammation by reducing the size of the retinochoroidal scar and preventing recurrence. The most common treatment for acute TRC is systemic administration of 1 or more antibiotics, usually given for 4 to 8 weeks. A large number of antibiotics have been described in the literature, and most agents are effective only against the active tachyzoite form of toxoplasma, and not the tissue-encysted bradyzoite form. Newer antimicrobial agents, including atovaquone and azithromycin, reduced the number of tissue cysts in animal models but have not prevented recurrences after short-term therapy in humans.[11,12] Recent publications also have reported intravitreal injection of clindamycin as an alternative to systemic treatment.[13] Some clinicians have added adjunctive corticosteroids to treat intraocular inflammation and its complications. Preventive strategies with systemic antibiotics for 1 year or more have been developed for infants who have congenital toxoplasmosis without retinochoroiditis, to reduce the risk of TRC, and similar strategies have been proposed for adults with recurrent TRC.[14,15] There are also reports of laser photocoagulation to treat active lesions.[16,17]

Resource Requirements

Most treatment regimens consist of a 4 to 8-week course of antibiotics. According to the literature, the most commonly used antibiotics are pyrimethamine, sulfadiazine, clindamycin, and combined trimethoprim and sulfamethoxazole. Sulfadiazine combined with pyrimethamine and corticosteroid is referred to as classic therapy, and it remains the most commonly used drug regimen.[10] The average wholesale cost ($0.58 per 25-mg tablet) of a 4-week supply of pyrimethamine (25 mg twice daily) is roughly $35.[18] A well-known side effect of pyrimethamine is bone-marrow suppression, which requires regular monitoring of baseline and serial leukocyte and platelet counts (most commonly performed every 2 weeks while receiving therapy), and this risk can be reduced by coadministration of folinic acid (most commonly 5 mg 2 to 7 times weekly). The estimated cost of a 4-week supply of folinic acid is approximately $40, and the average cost of 3 laboratory blood cell count tests (approximately $80 per test) is $240. The average wholesale cost ($2.50 per 500-mg tablet) of a 4-week supply of sulfadiazine (most commonly 1 g 4 times daily) is roughly $600.[19] The estimated cost of prednisone (60 mg daily for 30 days) is approximately $24. Therefore, the total cost of 4 weeks of treatment using classic therapy approaches $1000. Alternatively, the cost of a 4-week supply of clindamycin (most commonly 300 mg 4 times daily) is less than $300,[20] and the cost of a 4-week supply of combined trimethoprim and sulfamethoxazole (most commonly 160 mg and 800 mg, respectively, twice daily) is less than $40.[21]

Question for Assessment

The objective of this review is to address the following question: What are the outcomes and safety of interventions for TRC? The specific outcomes assessed are visual acuity, risk of 1 or more recurrences, and size of the lesion.

Description of Evidence

Literature searches were conducted last on July 20, 2011, in PubMed and the Cochrane Library databases, were limited to human studies, and had no date or language restrictions. The searches retrieved 275 unique citations. The search

strategy in the PubMed database (July 15, 19, and 20, 2011) was as follows:

1. ((*toxoplasmosis*, *ocular/drug therapy* [MeSH terms]) OR (*toxoplasmosis*, *ocular/prevention and control* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/surgery* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/therapy* [MeSH Terms]) OR (*chorioretinitis/drug therapy* [MeSH Terms]) OR (*chorioretinitis/prevention and control* [MeSH Terms]) OR (*chorioretinitis/surgery* [MeSH Terms]) OR (*chorioretinitis/therapy* [MeSH Terms])) AND (toxoplasm*[tiab]) Limits: Humans, Clinical Trial
2. ((*toxoplasmosis*, *ocular/drug therapy* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/prevention and control* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/surgery* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/therapy* [MeSH Terms]) OR (*chorioretinitis/drug therapy* [MeSH Terms]) OR (*chorioretinitis/prevention and control* [MeSH Terms]) OR (*chorioretinitis/surgery* [MeSH Terms]) OR (*chorioretinitis/therapy* [MeSH Terms])) AND (toxoplasm*[tiab]) AND ((*cohort studies* [MeSH Terms]) OR (*case control studies* [MeSH Terms]))
3. ((*toxoplasmosis*, *ocular/drug therapy* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/prevention and control* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/surgery* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/therapy* [MeSH Terms]) OR (*chorioretinitis/drug therapy* [MeSH Terms]) OR (*chorioretinitis/prevention and control* [MeSH Terms]) OR (*chorioretinitis/surgery* [MeSH Terms]) OR (*chorioretinitis/therapy* [MeSH Terms])) AND (toxoplasm*[tiab]) AND (series[tiab])
4. ((*toxoplasmosis*, *ocular/drug therapy* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/prevention and control* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/surgery* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/therapy* [MeSH Terms]) OR (*chorioretinitis/drug therapy* [MeSH Terms]) OR (*chorioretinitis/prevention and control* [MeSH Terms]) OR (*chorioretinitis/surgery* [MeSH Terms]) OR (*chorioretinitis/therapy* [MeSH Terms])) AND (toxoplasm*[tiab])
5. ((ocular toxoplasmosis[tiab]) OR (toxoplasma retinochoroiditis[tiab]) OR (toxoplasmic retinochoroiditis[tiab]) OR (toxoplasma chorioretinitis[tiab]) OR (toxoplasmic chorioretinitis[tiab]) OR (toxoplasmosis retinochoroiditis[tiab]))—867 references (7 references selected and imported)
6. ((toxoplasm*[tiab]) AND ((ocular[tiab]) OR (retinochoroid*[tiab]) OR (chorior*[tiab]))) AND ((antimicrobial[tiab]) OR (corticosteroid*[tiab]) OR (steroid*[tiab]) OR (photocoagulat*[tiab]) OR (coagulation*[tiab]) OR (cryotherapy[tiab]) OR (surgery[tiab]) OR (surgical[tiab]) OR (medicat*[tiab]) OR (intravitreal[tiab]) OR (oral[tiab]) OR (systemic [tiab]) OR (local[tiab]) OR (inject*[tiab]) OR (treat*[tiab]))—636 references (3 references selected and imported)
7. ((*toxoplasmosis*, *ocular/drug therapy* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/prevention and control* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/surgery* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/therapy* [MeSH Terms]) OR (*chorioretinitis/drug therapy* [MeSH Terms]) OR (*chorioretinitis/prevention and control* [MeSH Terms]) OR (*chorioretinitis/surgery* [MeSH Terms]) OR (*chorioretinitis/therapy* [MeSH Terms])) AND (toxoplasm*[tiab]) AND (review[tiab])
8. ((*toxoplasmosis*, *ocular/drug therapy* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/prevention and control* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/surgery* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/therapy* [MeSH Terms]) OR (*chorioretinitis/drug therapy* [MeSH Terms]) OR (*chorioretinitis/prevention and control* [MeSH Terms]) OR (*chorioretinitis/surgery* [MeSH Terms]) OR (*chorioretinitis/therapy* [MeSH Terms])) AND (toxoplasm*[tiab])
9. ((*toxoplasmosis*, *ocular/drug therapy* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/prevention and control* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/surgery* [MeSH Terms]) OR (*toxoplasmosis*, *ocular/therapy* [MeSH Terms]) OR (*chorioretinitis/drug therapy* [MeSH Terms]) OR (*chorioretinitis/prevention and control* [MeSH Terms]) OR (*chorioretinitis/surgery* [MeSH Terms]) OR (*chorioretinitis/therapy* [MeSH Terms])) AND (toxoplasm*[tiab]) AND (survey*[tiab])

The search strategy was as follows in the Cochrane Library (July 18, 2011):

1. MeSH descriptor Toxoplasmosis, Ocular explode all trees—11 references
2. MeSH descriptor Chorioretinitis explode all trees AND (toxoplasm*):ti,ab,kw
3. (ocular toxoplasm*):ti,ab,kw or (toxoplasm* AND retinochoroiditis):ti,ab,kw or (toxoplasm* AND chorioretinitis)

The first author (S.J.K.) reviewed the abstracts of these articles and selected 35 of possible clinical relevance that then were obtained in full text (Fig 1). One additional article was identified from the reference list of the Cochrane Review.[22] Of these 36 articles, 11 were deemed sufficiently relevant or of interest and were reviewed by the panel methodologists. The methodologists used a rating scale based on that developed by the British Centre for Evidence-Based Medicine[23] and assigned one of the following ratings of level of evidence to each of the selected articles. A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies and poor-quality randomized studies; and a level III rating was assigned to case series, case reports, and poor-quality cohort and case-control studies.

Of the 36 studies reviewed, 8 of the 11 studies that were deemed sufficiently relevant were prospective randomized studies; 3 were randomized comparisons of antibiotic treatment versus placebo or no treatment[15,24,25] (Table 1) and 5

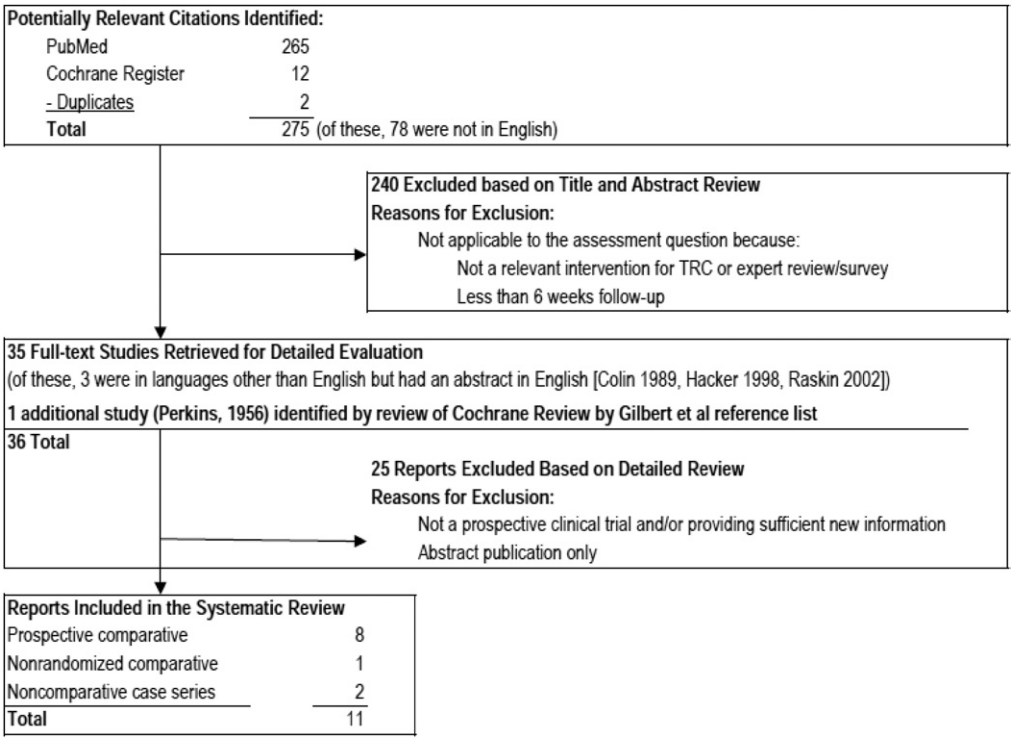

Figure 1. Diagram showing studies evaluated for inclusion in the interventions for toxoplasma retinochoroiditis Ophthalmic Technology Assessment. TRC = toxoplasma retinochoroiditis.

were randomized comparisons of different antibiotic regimens[13,26–29] (Table 2).

All 3 placebo or no-treatment controlled studies were rated as level II evidence because of methodologic limitations, which greatly affected interpretation of the study results. In the study by Perkins et al,[25] there was uncertainty about the underlying diagnosis of TRC in many of the patients in addition to a lack of rigorous and objective assessment of clinical response. The study by Acers[24] similarly had a lack of rigorous assessment of outcomes in addition to a small sample size. The study by Silveira et al[15] was unmasked and had a lack of uniform documentation of baseline and recurrent disease by fundus photography. In addition, the study was conducted in Brazil, where the strain of *T gondii* is thought to be more virulent and may cause more frequent recurrences and severe lesions when compared with strains seen in North America or Europe.[30] Therefore, the results of the study may not be applicable directly to other populations. Most importantly, none of the above studies provided results of visual acuity or changes in lesion size, which were primary outcome measures of this assessment.

Evidence quality of the 5 clinical trials of different antibiotic regimens was limited by relatively small sample sizes and

Table 1. Prospective Randomized Studies Comparing Antibiotic Treatment versus Placebo or No Treatment

Study	No. of Patients	Visual Acuity Outcome	Recurrent Lesions	Change in Lesion Size	Adverse Effects
Perkins et al[25]	98 (positive toxoplasma reaction)	N/A	N/A	N/A	Pyrimethamine was associated with drop in hemoglobin of 5% or more in 47% of patients
Acers[24]	20	N/A	No difference at 2 yrs	N/A	3 of 10 patients receiving pyrimethamine/trisulfapyrimidine experienced adverse reactions; 1 patient experienced severe thrombocytopenia
Silveira et al[15]	124*	N/A	At 14 mos recurrence was 6.6% in treated patients and 24% in untreated patients	N/A	Trimethoprim/sulfamethoxazole discontinued in 4 of 61 patients (7%) because of mild drug reactions

N/A = not available.
*Patients with chronic infection were treated prophylactically to decrease recurrences.

Table 2. Prospective Randomized Studies Comparing Different Antibiotic Regimens

Study	No. of Patients	Comparison
Only abstract in English		
Colin and Harie[27]	29	Pyrimethamine/sulfadiazine vs. subconjunctival injections of clindamycin
Raskin et al[28]	49	Sulfadiazine/pyrimethamine/corticosteroid vs. trimethoprim/sulfamethoxazole/corticosteroid
Study published in English		
Bosch-Driessen et al[26]	46	Pyrimethamine/azithromycin/corticosteroid vs. pyrimethamine/sulfadiazine/corticosteroid
Soheilian et al[29]	59	Pyrimethamine/sulfadiazine/prednisolone vs. trimethoprim-sulfamethoxazole/prednisone
Soheilian et al[13]	68	Intravitreal clindamycin/dexamethasone vs. pyrimethamine/sulfadiazine/prednisolone

the absence of double masking. These studies were rated as level II evidence. The remaining 3 studies included a nonrandomized prospective trial[8] and 2 noncomparative case series[16,31] and were all rated as level III evidence.

Published Results

Randomized Studies with Placebo or No Treatment Control Group

Perkins et al[25] reported the effects of 4 weeks of treatment with pyrimethamine compared with inert tablets in patients with acute uveitis from any cause. Results for subgroups of patients with anterior uveitis, posterior uveitis, and panuveitis who showed positive or negative results for toxoplasma antibodies were randomized to either pyrimethamine or placebo. The study was double-masked, but masking may have been compromised by a higher percentage of hemoglobin levels that were reduced more than 5% in patients taking pyrimethamine. The primary outcome was defined vaguely and was categorized as improved or not improved after assessment of the clinical condition, without attempt to quantify the degree of improvement. No information was provided on visual acuity, lesion size, rates of recurrence, or loss to follow-up. The study demonstrated a statistically significant improvement in cases of uveitis having positive toxoplasma antibodies treated with pyrimethamine, but the authors estimated that only 25% of these cases may have been the result of active TRC (level II evidence). It was unclear whether testing for other causes of uveitis such as syphilis or tuberculosis was performed. Pyrimethamine treatment resulted in a drop in hemoglobin of 5% or more in 47% of patients, but only 1 patient had to discontinue treatment early because of anemia.

Acers[24] compared the effect of 8 weeks of combined pyrimethamine and trisulfapyrimidine and corticosteroid versus lactose capsules and corticosteroid in patients with acute TRC. The diagnosis of TRC was made in the setting of active retinitis, positive intradermal toxoplasmin skin test results, positive Sabin methylene blue-dye test results, and lack of significant clinical or laboratory evidence of other causes. Inactivity was determined clinically by the absence of anterior chamber reaction, clearing of the vitreous, and resolution of the retinal inflammation. The study was double-masked, and a total of 20 patients (10 in each group) were randomized to treatment or placebo. Regardless of therapy, all patients showed progressive improvement by 8 weeks (level II evidence). Three of the 10 patients treated with combined pyrimethamine and trisulfapyrimidine experienced side effects, and 1 of these patients experienced severe thrombocytopenia requiring early cessation of treatment. Over a 2-year period, there were 2 recurrences, 1 in each group.

In a prospective, randomized, open-labeled study, Silveira et al[15] determined the long-term effect of prophylactic combined trimethoprim and sulfamethoxazole treatment compared with no treatment on rates of recurrence. A total of 124 patients with a history of recurrent TRC were randomized to treatment with combined trimethoprim (160 mg) and sulfamethoxazole (800 mg), 1 tablet every 3 days (61 patients), or to observation without treatment (63 patients) and were followed up monthly for up to 20 months for clinical signs of recurrence. Serologic testing confirmed the presence of anti−*T gondii* immunoglobulin G antibodies in all patients before enrollment. Medications were administered in an unmasked fashion, and patients in the control group received no treatment. The primary end point of the study was development of recurrent TRC defined clinically as a new focus of retinal inflammation either adjacent to or remote from a pre-existing retinochoroidal scar. All patients were examined monthly by 1 ophthalmologist who was unmasked. Six patients (10%) in the treatment group and 4 patients (6%) in the control group were lost to follow-up. In the treatment and control groups, recurrent TRC developed in 4 patients (7%) and 15 (24%) patients, respectively (level II evidence). Compliance with treatment was determined by patient interviews and monitoring of dispensed tablets to patients in the treatment group. Treatment was discontinued prematurely in 4 patients because of mild drug reactions.

Randomized Antibiotic Comparison Studies

For 2 studies of the 5 randomized comparisons of different antibiotics, only the abstracts were available in English for review. The study by Colin and Harie[27] was conducted in 29 patients and compared the efficacy of combined pyrimethamine and sulfadiazine given with subconjunctival injec-

tions of clindamycin. After 14 months of follow-up, there was no difference between groups in terms of visual acuity or recurrence rates (21% in the clindamycin group and 36% in the combined pyrimethamine and sulfadiazine group). No information was provided in the abstract on masking, change in lesion size, loss to follow-up, or whether corticosteroids were used. Raskin et al[28] evaluated the efficacy of combined pyrimethamine and sulfadiazine versus combined trimethoprim and sulfamethoxazole in 49 patients. All patients received adjuvant therapy with oral corticosteroids. The primary outcome was time to resolution of active retinochoroiditis. Faster resolution was observed with combined pyrimethamine and sulfadiazine (28 days) compared with combined trimethoprim and sulfamethoxazole (35 days) treatment. No details were given on how resolution of retinochoroiditis was determined. Similarly, no information was provided on visual acuity, lesion size, or rates of recurrence.

The 3 remaining antibiotic comparison studies were available in English for complete review. Bosch-Driessen et al[26] compared the time to resolution of intraocular inflammation, lesion size, and visual acuity before and after treatment between treatment with combined pyrimethamine and azithromycin (24 patients) and with combined pyrimethamine and sulfadiazine (22 patients). The results of the study demonstrated no significant differences between treatment groups for the primary outcomes, but adverse effects were more frequent in the combined pyrimethamine and sulfadiazine group (level II evidence). Soheilian et al[29] compared change in lesion size, visual acuity, and rate of recurrence between treatment with combined pyrimethamine and sulfadiazine (29 patients) and with combined trimethoprim and sulfamethoxazole (30 patients). The results of the study demonstrated no significant differences between the treatment groups with respect to the primary outcome and similar rates of adverse events (level II evidence). Another study by Soheilian et al[13] reported on the efficacy of intravitreal injection of clindamycin and dexamethasone compared with classic systemic therapy using combined pyrimethamine, sulfadiazine, and prednisone. A total of 68 patients were enrolled, and 34 were randomized to each treatment group. The primary outcome measure was change in retinochoroidal lesion size 6 weeks after initiation of treatment. The study reported no difference in lesion size or visual acuity between treatment groups, but patients with immunoglobulin M−positive antitoxoplasma serum antibodies responded better to systemic treatment with respect to the primary outcome (level II evidence). There were no major adverse reactions in the intravitreal clindamycin group, but 2 adverse reactions occurred in the systemic treatment group.

Interpretation of the antibiotic comparison studies above is based on the assumption that treatment with combined pyrimethamine and sulfadiazine has a beneficial effect for all patients with TRC, which remains unproven.

Nonrandomized Prospective Study

In a nonrandomized study of 149 patients, Rothova et al[8] reported a positive relationship between treatment with combined pyrimethamine and sulfadiazine and reduction of lesion size (level III evidence). However, no difference was observed in the duration of inflammation between treated and untreated patients, and the most important factor predicting the duration of inflammation was the size of the initial retinal lesion, independent of treatment. There was also a high frequency of adverse effects associated with treatment that resulted in discontinuation in 26% of patients receiving combined pyrimethamine, sulfadiazine, and corticosteroid; 17% of patients receiving combined clindamycin, sulfadiazine, and corticosteroid; and 4% of patients receiving combined trimethoprim, sulfamethoxazole, and corticosteroid. No significant difference in the recurrence rate was observed between treated and untreated patients.

Other Studies of Interest

A noncomparative case series reported on quadruple therapy consisting of 3 different antibiotics and corticosteroid for the treatment of TRC (level III evidence).[31] A total of 37 eyes of 36 patients received combined treatment with pyrimethamine, trisulfapyrimidine, clindamycin, and prednisone. An improvement in vision was observed in 20 eyes (54%) within 2 weeks and in 30 eyes (81%) within 3 weeks. Four patients demonstrated a skin rash presumed to be secondary to trisulfapyrimidine therapy. Desmettre et al[16] reported on recurrence rates of 35 patients with TRC whose lesions were treated with laser photocoagulation (level III evidence). Recurrence rates occurred in 13% of eyes at 1 year, 20% at 2 years, and 33% at 4 years, and they increased steadily thereafter with longer follow-up. The authors were unable to observe a preventive effect of laser photocoagulation on recurrence rates of TRC.

In conclusion, despite the common practice of treating TRC with systemic antibiotics, there are no randomized controlled trials demonstrating that antibiotic treatment improves long-term visual outcomes. In addition, there is only 1 study[15] that provides level II evidence that prophylactic treatment with combined trimethoprim and sulfamethoxazole reduces the rate of recurrence in Brazilian patients with a history of recurrent TRC. The conclusions of this particular study should be interpreted cautiously, however, because the study investigators and subjects were unmasked and other strains of *T gondii* may respond differently to treatment. Equally important, there is no convincing evidence to date that treatment decreases the severity of intraocular inflammation or duration of disease for all patients. A Cochrane review of treatment of TRC with antibiotics reported similar conclusions about the lack of evidence for treatment of acute TRC and weak evidence for recurrent disease.[22]

The lack of conclusive clinical evidence of the effectiveness of antibiotics is in contrast to data from animal studies that demonstrate that antimicrobial drugs are highly effective for treatment of active toxoplasmosis. Although a treatment effect has been difficult to find in immunocompetent hosts, the benefit of treatment and prevention of toxoplasmosis infection has been shown more convincingly in immunosuppressed patients with AIDS. Furthermore, studies have suggested that long-term treatment of newborns

with congenital toxoplasmosis for up to 1 year using pyrimethamine and sulfadiazine reduced the risk of developing TRC when compared with historical untreated controls.[14,15] Finally, TRC has a broad heterogenous clinical spectrum, extending from small peripheral active lesions that frequently resolve spontaneously to larger progressive ones, which eventually may result in markedly decreased vision.[6,7,32]

Friedmann and Knox[7] reported that lesions of more than 1 disc area were associated with worse visual outcomes. This observation was supported by a large prospective study by Rothova et al,[8] in which the most important predictor of duration of inflammation was the initial size of the retinochoroidal lesion. Furthermore, prospective studies have demonstrated a relationship between antibiotic treatment and reduction of final lesion size.[8,29] However, the lack of proper controls raised the possibility that these improvements could be part of natural history.

There are also no randomized controlled studies evaluating the treatment effect of corticosteroids, but several publications described poor outcomes in patients who received systemic or local corticosteroid therapy in the absence of antibiotic treatment.[6] Therefore, it seems prudent to recommend concomitant antibiotic treatment when corticosteroids are administered. Experience with nonmedical therapies also is limited. The treatment benefit of photocoagulation of active lesions is unproven. Vitrectomy surgery also has been performed in patients with active TRC, but typically in the setting of diagnosis or treatment of complications.[10]

Although there continues to be uncertainty about the treatment benefit of antibiotics and corticosteroids, available evidence shows that short-term treatment does not prevent recurrence. Therefore, programs for primary prevention have focused on pregnant women to prevent congenital transmission. Greater emphasis is needed to reduce postnatally acquired cases by eliminating exposure to recognized sources of infection, such as undercooked meat and water contaminated with oocysts from cat feces.

In addition to treatment outcomes, this assessment also focused on safety. Rates of reported adverse reactions depended largely on the antibiotic regimen used, but were relatively common overall. The combination of pyrimethamine and sulfadiazine was characterized by frequent and severe side effects, leading to discontinuation of treatment in up to 25% of patients in some studies, mostly as a result of bone-marrow suppression and allergic reactions. The combination of trimethoprim and sulfamethoxazole seems to be better tolerated and is considerably less expensive than classic therapy, but it infrequently can cause severe life-threatening hypersensitivity reactions, such as Stevens-Johnson syndrome.

In conclusion, there is a lack of level I evidence to support routine antibiotic or corticosteroid treatment for all immunocompetent patients with acute TRC. Other nonmedical treatments also remain unproven. There is level II evidence from a single study suggesting that long-term prophylactic treatment with combined trimethoprim and sulfamethoxazole may reduce recurrences in patients with recurrent TRC. The lack of large, randomized studies providing evidence for treatment benefit of active TRC should be viewed with caution and should not serve as an absolute contraindication to therapy in patients at high risk of vision loss.

Future Research

Randomized placebo-controlled trials are needed to determine the therapeutic efficacy of antibiotic treatment for acute or recurrent episodes of TRC. Such studies will be difficult to perform because of the heterogeneity of the disease, presence of confounding factors, and lack of validated outcome measures that accurately reflect treatment benefit. Despite these challenges, future studies should attempt to ensure uniform and rigorous masked assessment of long-term visual outcomes, rates of recurrence, duration of symptoms, and severity of inflammation. Similarly designed studies are needed to determine the treatment benefit of corticosteroids. Emphasis should be placed on interventions with minimal risk of adverse reactions and low treatment cost.

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