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Ocular toxoplasmosis: A review of current treatment options

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HIGHLIGHTS

Toxoplasmosis is an under-recognized yet leading cause of posterior uveitis worldwide. Apart from standard treatment, innovative approaches present promising future treatment options.

ABSTRACT

Ocular toxoplasmosis (OT), a global health concern due to the protozoan *T. gondii*, disproportionately affects immunocompromised individuals, causing severe eye infections and potential vision loss. This review aims to evaluate current treatment options, highlighting challenges in managing both congenital and acquired forms of the infection. Our analysis synthesizes findings from 21 recent studies and a key specialty textbook, selected through systematic searches on databases including PubMed and ScienceDirect, focusing on treatments developed since 2018 to ensure relevance in the field of OT management. While diagnosis relies heavily on clinical assessments, advanced imaging like optical coherence tomography and fluorescein angiography, as well as serological and PCR testing, have improved detection. Treatment primarily involves antiparasitic and antibacterial drugs, yet standard protocols, such as pyrimethamine and sulfadiazine combinations, often fail due to severe side effects and high recurrence rates. The emergence of drug-resistant strains complicates therapy, underscoring the necessity for novel treatment approaches. Recent advancements suggest potential in mitochondrial inhibitors and histone deacetylase inhibitors, yet further research is essential to minimize toxicity and enhance specificity. OT management is hindered by the complexity of its clinical presentation and the suboptimal efficacy of traditional treatments. Personalized treatment strategies, considering patient history and local drug availability, are critical for improving outcomes in those afflicted by this debilitating infection.

Key words: ocular toxoplasmosis, toxoplasmosis, *Toxoplasma gondii*, uveitis, retinitis, diagnosis, treatment

INTRODUCTION AND OBJECTIVE

Ocular toxoplasmosis (OT) is an infectious disease induced by the intracellular protozoan *T. gondii*, which affects both humans and warm-blooded animals. It is estimated that roughly ⅓ of the global population is chronically infected, although the prevalence and sources of infection vary widely. The disease is typically asymptomatic, complicating early detection [1]. The main route of infection involves ingestion of oocysts from contaminated soil, sand, fruits, vegetables and water, as well as consumption of tissue cysts in raw or undercooked meat. The protozoan can exist in 3 forms: tachyzoites, bradyzoites and oocytes, all of which have the capacity of infecting the host [2]. The aforementioned parasite is capable of breaching the blood-retinal barrier, leading to ocular involvement. Upon entering the eye, the protozoan may persist in a dormant state within the retina, with the potential to reactivate during periods of low immunity [2].

Ocular toxoplasmosis (OT) is the leading cause of posterior uveitis worldwide, particularly affecting immunocompromised individuals. It is estimated that 30–50% of cases are due to toxoplasmosis infection. The hallmark lesion of the disease is focal necrotizing retinitis, with overlying vitritis which can progress into hyperpigmented retinochoroidal scars. Additionally, macular involvement may occur, posing a significant risk of permanent deterioration of vision [3]. In the past, the disease was associated with a recurrent congenital infection. However, the infection may be either congenital or acquired, with the acquired form being more prevalent. The congenital form arises when the fetus is infected through the placental bloodstream, while in acquired infections, the parasite is transmitted via the gastrointestinal tract. The congenital form tends to be more severe, frequently leading to bilateral macular lesions and retinal damage, whereas the acquired form typically presents with focal retinitis near chorioretinal scars, which may increase the risk of blindness [2]. The congenital form of the disease can be associated with the presence of cataract, chorioretinitis, microphthalmos and optic atrophy in newborns [4]. The acquired form of the infection develops within few days post infection and remains asymptomatic in 80% of immunocompetent individuals [5]. However, both forms of the disease can cause severe ocular damage and deterioration of vision [6]. Additionally, the disease is known for its potential to recur throughout patient's life [3].

REVIEW METHODS

This review is based on a thorough analysis of 21 studies and a renowned specialty textbook, carefully selected from open-access sources through systematic searches conducted in PubMed, ResearchGate, ScienceDirect and Google Scholar. The search strategy emphasized therapeutic approaches to ocular toxoplasmosis, prioritizing recent publications, primarily from 2018 onward, to provide a contemporary overview of emerging treatment options. Older articles were excluded unless their content remained relevant and aligned with current knowledge.

STATE OF KNOWLEDGE

Diagnosis

Diagnosis of ocular toxoplasmosis (OT) is based on a detailed clinical assessment and advanced imaging methods. The key element of OT is the presence of necrotic foci in the retina, which are often associated with previous retinal scarring, leading to active inflammatory retinopathy. Typical symptoms include vitreous opacity ("headlight in the fog" sign) and retinal necrosis, often located at the periphery of old lesions. Additionally, patients may have adhesions and other signs of previous infections, such as increased intraocular pressure and anterior uveitis [7, 8].

Imaging diagnostics, including fluorescein angiography (FA) and optical coherence tomography (OCT), are especially important in assessing the extent of damage and monitoring treatment. OCT allows for the analysis of retinal thickness and the severity of necrosis, while FA helps identify vascular leakage and damage to the retinal pigment epithelium [9].

The presence of an active inflammatory focus at the borders of old scars is often identified using these diagnostic tools. Serological tests, such as IgG and IgM antibody levels against *T. gondii*, are an important part of the diagnostic process. PCR testing can be used in difficult cases or in immunocompromised patients, especially when standard tests give equivocal results. In such situations, PCR testing performed on samples of fluid from the anterior chamber of the eye or vitreous humor can help detect the parasite's DNA [10].

Although the clinical picture is key to diagnosis, the disease can present atypically, especially in immunosuppressed patients, which can lead to diagnostic errors and delayed treatment [11]. In such cases, it is important to combine clinical, imaging, and laboratory tests to make the correct diagnosis and choose the appropriate treatment.

Prevention

Many governments provide guidelines to prevent toxoplasmosis, with the U.S. CDC offering detailed advice such as feeding cats commercial food, cleaning litter daily, and cooking meat properly. Preventative education is emphasized, especially for pregnant women and immunocompromised individuals, though the effectiveness of these educational programs varies. France is noted for its success in managing toxoplasmosis through screening and education, though cost-effectiveness is debated.

Efforts to reduce *T. gondii* contamination in food focus on biosecurity and post-harvest measures. Pre-harvest strategies aim to reduce contamination on farms by controlling cat and rodent populations. Post-harvest treatments, like freezing or irradiation, can inactivate cysts in meat, but consumer acceptance remains a challenge. Contaminated water has also been a major source of toxoplasmosis outbreaks, with filtration systems necessary as oocysts are resistant to standard water treatment methods.
While some interventions, like vaccination of animals, are being explored, they are costly and difficult to implement widely [12].

Current chemotherapeutical treatment and folic acid inhibitors

The treatment for toxoplasmosis mainly involves antiparasitic and antibacterial drugs, with therapeutic strategies varying based on the disease state and the host's immune system. In congenital toxoplasmosis, the first-line therapy is a combination of pyrimethamine and sulfadiazine, which blocks folate biosynthesis in the parasite, inhibiting nucleic acid synthesis. Folinic acid is added to reduce side effects such as bone marrow suppression, although risks like neutropenia and teratogenic effects remain. Pregnant women suspected of toxoplasmosis are treated prophylactically with spiramycin, but if fetal infection is confirmed, treatment shifts to pyrimethamine/sulfadiazine.
In immunocompetent patients, treatment is usually unnecessary, but severe cases, especially in regions like South America, are treated with pyrimethamine combined with sulfadiazine, clindamycin, or azithromycin, among others. Chronic toxoplasmosis remains untargeted by these therapies, and reactivation occurs in immunocompromised patients, such as those with HIV or organ transplants, leading to serious complications like toxoplasmic encephalitis. For HIV patients, sulfadiazine and pyrimethamine are standard treatments, though side effects are common. Anti-retroviral therapy significantly improves survival. For transplant patients, prophylactic treatment is often recommended, though there is no standard effective therapy [5].
However, the efficacy of antibiotic treatment has been investigated, and numerous studies have concluded that antibiotic therapy is generally not optimally successful. Furthermore, there is still no conclusive evidence identifying the most effective treatment regimen.
Difficulties in treating OT with antibiotics stem from extended treatment durations of 4–6 weeks, which increase the risk of complications. A review of 2975 patients across various forms of toxoplasmosis showed a significant rate of adverse events, with up to 37% requiring treatment changes due to side effects. For OT, side effects, including bone marrow suppression, were common, emphasizing the need for blood monitoring during pyrimethamine-based treatments. The use of corticosteroids in OT treatment remains debated, with questions surrounding their effectiveness and optimal dosage when combined with antiparasitic therapy. A recent meta-analysis of randomized trials in immunocompetent individuals found no studies directly evaluating the impact of corticosteroids alongside antiparasitics, despite their common use. Recurrences of OT pose a risk of permanent eye damage and are influenced by factors such as age, geography, genetics, and immune response. Younger patients have a higher recurrence risk, with 55–60% experiencing repeat episodes. While recurrence rates decrease with age, the impact of treatment on recurrence timing remains unclear. A German registry found that corticosteroid monotherapy without antibiotics shortened recurrence-free intervals [13].
A meta-analysis by Feliciano-Alfonso et al. assessed the safety and effectiveness of different antibiotic treatments for toxoplasmosis. The study reviewed 10 studies, with 4 included in the meta-analysis. The interventions were divided into 3 groups: intravitreal clindamycin versus pyrimethamine + sulfadiazine, trimethoprim + sulfamethoxazole versus other antibiotics, and other approaches. The results slightly favored intravitreal clindamycin in visual acuity (MD = 0.10 logMAR), but the difference was not clinically significant. No other outcomes showed meaningful differences between treatment groups. The studies were prone to performance bias, and the overall quality of evidence was low to very low. Since no treatment proved to be superior, according to the author the choice of therapy should be individualized, taking into account safety (with azithromycin being the safest), medical history (e.g., sulfa allergies), and the availability of drugs in the healthcare system. While there is no agreement on the best treatment for OT, therapy should include at least two antibiotics possibly combined with corticosteroids [14].

Further treatment methods

Apart from the standard treatment trimethoprim-sulfamethoxazole is a common alternative for OT due to its safety, accessibility, and affordability. Studies show that combining it with prednisolone is safer and more effective than traditional treatments. Recent alternatives include systemic or intravitreal antibiotics, like clindamycin and dexamethasone, which have shown effective control of retinal chorioretinitis. While antibiotics may lower the risk of recurrent *T. gondii*-related choroiditis, evidence supporting improved patient outcomes is limited. Experimental studies have found atovaquone (ATQ) and azithromycin effective against OT, though not in preventing recurrence, possibly due to drug resistance in *T. gondii* [1].
The mitochondrial electron transport chain in *T. gondii* plays a critical role in ATP production and pyrimidine biosynthesis. ATQ, a well-known antiparasitic, targets the Q_o

site of complex III in the mitochondrial electron transport chain in *T. gondii*, disrupting electron transfer and ATP synthesis. Despite its efficacy against tachyzoites and tissue cysts, clinical trials have shown mixed results in preventing infection relapse, suggesting incomplete cyst elimination [12].

Choroidal neovascularization (CNV) is a common complication of OT and inflammatory conditions, requiring careful management to preserve visual acuity. Intravitreal anti-VEGF therapy, particularly bevacizumab, has proven effective across various cases, improving or stabilizing vision with minimal complications. While CNV causes vary (toxoplasmic vs. inflammatory), all studies highlight the value of combining anti-VEGF agents with anti-inflammatory treatments for optimal outcomes, with differences in supporting therapies and accessibility considerations [15–18].

Potential treatment methods

Recent in vitro and in vivo study results suggest that exosomes have been investigated as an efficient drug delivery system. Loading ATQ into exosomes enhances its effect against *T. gondii*, suggesting a new strategy for improving the effectiveness of ATQ against both the acute and chronic phases of *T. gondii* [19].

Newer complex III inhibitors, such as the endochin-like-quinolone (ELQ-271, ELQ-316) series, show improved potency and specificity compared to ATQ. Resistance to inhibitors targeting the Q_o and Q_i sites, due to mutations in cytochrome b, remains a challenge. Combining inhibitors that target both sites, such as ELQ-334 and ATQ, could slow resistance development and improve treatment outcomes, as seen in related apicomplexan infections [12].

Histone deacetylases (HDACs) are promising targets for the development of potential drugs targeting *T. gondii*. HDACs regulate gene expression and chromatin structure by controlling histone acetylation, and their inhibition can lead to cell death in parasites. Differences between parasite and human HDACs present opportunities for selective targeting, reducing toxicity in host cells. Various HDAC inhibitors (HDACi) show efficacy in inhibiting parasite growth, including natural compounds like trichostatin A (TSA) and synthetic derivatives such as suberoylanilide hydroxamic acid (SAHA), while SAHA demonstrated better selectivity and efficacy against *T. gondii* [20]. Tubastatin A (TST) is another HDCAi which shows sustained anti-proliferative effects but also impairs mitochondrial membrane potential, while SAHA induces mitochondrial fragmentation [21].

TABLE 1

Summary of therapeutic strategies for ocular toxoplasmosis [12, 13, 19–22].

Preventive measures	1. Pet care and hygiene: • avoid raw or undercooked meat, prefer canned food • use a litter box and change litter daily while wearing disposable gloves • keep cats indoors. 2. Personal hygiene and food safety: • wear gloves when gardening or handling soil • wash fruits and vegetables thoroughly before eating • freeze meat for at least 2 days before cooking • cook meat to safe temperatures • clean all kitchen tools and surfaces that come into contact with raw food • wash hands thoroughly after contact with soil or sand, handling uncooked food, interaction with pets or cleaning pet waste (e.g., cat litter) • avoid drinking untreated water.
Vaccination	1. Vaccination of cats to prevent oocyst excretion is conceivable, a live attenuated vaccine has been tested on pig farms. 2. A commercial vaccine against *T. gondii* designed to prevent abortion in sheep is available, but not considered suitable for administration to humans. 3. There are no reports of *T. gondii* vaccine studies in humans.
Chemotherapeutics and folic acid inhibitors	1. First-line therapy: pyrimethamine + sulfadiazine. 2. Alternatively: pyrimethamine + sulfadiazine, clindamycin, or azithromycin. 3. Pregnant women: prophylactic spiramycin.
Alternative treatment methods	1. Trimethoprim-sulfamethoxazole. 2. Atovaquone. 3. Choroidal neovascularization: bevacizumab (intravitreal anti-VEGF therapy).
Corticosteroids	1. Effectiveness in combination with antibiotics is debated. 2. Use alone seems to be associated with a shorter time to recurrence.
Experimental treatment	1. Atovaquone-loaded macrophage-derived exosomes (murine model). 2. Endochin-like-quinolones (murine model). 3. Histone deacetylases (murine in-vitro and in-vivo studies): trichostatin A, suberoylanilide hydroxamic acid, tubastatin A. 4. Protein kinase inhibitors; various in vitro and in vivo studies targeting TCA cycle regulation, FAS II pathway, pantothenate pathway, cell cycle regulation and glycolysis of *T. gondii*.

Further research on HDAC inhibitors is needed to enhance their selectivity, bioavailability, and efficacy in treating parasitic infections. Combining these inhibitors with other therapies could improve outcomes. Although HDAC inhibitors are effective in disrupting parasite growth, challenges with toxicity and specificity persist. Targeting specific histone modifications in *T. gondii* may lead to safer and more effective treatments for toxoplasmosis [20].

Protein kinases are promising targets for developing selective inhibitors against protozoan pathogens like *T. gondii*. Their structural differences and unique metabolic pathways, compared to human cells, allow for safer and more effective therapies. Key targets include kinases involved in glycolysis, such as PFK, PGK, and PYK. Inhibiting PFK2 disrupts early glycolysis, leading to toxic effects on the parasite, while acetylation sites in PGK offer opportunities for specific drug targeting. Additionally, inhibiting PYK1 and PYK2 suppresses glycolysis and apicoplast function, disrupting essential metabolic pathways. Targeting kinases in the pantothenate pathway could also impact crucial processes like the TCA cycle and FAS II biosynthesis [22].

Summary of therapeutic strategies for ocular toxoplasmosis is presented in table 1.

CONCLUSIONS

Ocular toxoplasmosis remains a significant cause of posterior uveitis worldwide, with potentially severe outcomes for vision. Despite advances in diagnosis through imaging techniques like OCT and FA, and the use of serological and PCR tests, treatment remains challenging due to the disease's complex pathology and variable response to antibiotics. Standard therapies, such as pyrimethamine–sulfadiazine combinations, often face limitations due to side effects and incomplete cyst eradication, leading to recurrence risks. Emerging treatments, including novel mitochondrial inhibitors and HDAC inhibitors, offer promise but require further research to improve specificity and reduce toxicity. Additionally, anti-VEGF therapy shows potential in managing OT-related complications like choroidal neovascularization. Preventative measures, particularly in vulnerable populations, and personalized treatment plans based on patient history and drug availability, are crucial for effective management. Future therapies should target novel molecular pathways to enhance treatment efficacy and patient outcomes.

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