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Therapeutic alternatives for the treatment of ocular toxoplasmosis

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ABSTRACT

Ocular toxoplasmosis is caused by *Toxoplasma gondii*, inducing retinochoroiditis. It is the leading cause of infectious posterior uveitis worldwide. Its treatment is based on oral drug administration. However, the blood–ocular barrier systems make the penetration of therapeutic drug concentrations within the eye difficult, limiting the effectiveness of treatments. In this context, ocular drug delivery systems represent therapeutic alternative for the treatment of ocular toxoplasmosis. In this study, a review of clinical manifestations, diagnosis, treatment, and perspectives regarding the treatment of ocular toxoplasmosis was conducted. A search was carried out on ScienceDirect, Scopus, Web of Science, PubMed, and SciELO, and the following keywords were used: toxoplasmosis, ocular toxoplasmosis, toxoplasmic retinochoroiditis, and congenital toxoplasmosis; and Boolean operators, associated with other keywords, such as epidemiology, ocular toxoplasmosis diagnosis, ocular toxoplasmosis treatment, and ocular toxoplasmosis perspectives, were applied. In conclusion, ocular toxoplasmosis still lacks effective treatment. Therefore, it is essential to develop new molecules and/or new drug delivery systems capable of releasing therapeutic doses of anti-*Toxoplasma* drugs directly in the posterior segment of the eye, for an extended period, since complications resulting from the disease may shorten the productive life of individuals and may even lead to blindness.

INTRODUCTION

Ocular toxoplasmosis is caused by *Toxoplasma gondii*, an intracellular parasite. *T. gondii* induces the formation of lesions in the delicate ocular tissues of the posterior segment of the eye. These lesions lead to an inflammatory process, mainly in the retina and choroid (retinochoroiditis), inducing uveitis. Ocular toxoplasmosis is the major cause of infectious uveitis worldwide (Oréfice *et al*., 2005). In Brazil, 80% of the infectious posterior uveitis cases were associated with ocular toxoplasmosis (Oréfice *et al*., 2005). When the inflammatory process resolves, the lesion heals. However, dormant *T. gondii* remain at the edge of healed lesions and, after a variable period of months or years, the parasite becomes active, causing new lesions adjacent to the old scars. Approximately, two-thirds of the affected patients experience the recurrence of ocular toxoplasmosis (Guex-Crosier, 2009; Santos *et al*., 2015; Tanaka *et al*., 2014). The recurrence of the inflammatory process results in the reestablishment of severe uveitis. Consequently, the irreversible damage to ocular tissues leads to reduced visual acuity or blindness.

Treatment of ocular toxoplasmosis involves oral administration of antibiotics and anti-inflammatory drugs. However, the blood–retina and blood–aqueous barriers protecting the eye limit the therapeutic concentrations from systemic drugs in the posterior segment of the eye. As a result, subtherapeutic concentrations reach the eye; therefore, ocular toxoplasmosis progresses. In addition, these drugs may induce side effects and/or toxicity, reducing patient's compliance to therapy.

Currently, few researchers have been investigating new therapeutic strategies to treat ocular toxoplasmosis in order to overcome some of the disadvantages associated with conventional therapies. Among these strategies, implantable polymeric devices, intravitreal injections. Although intravitreal injections are not yet commercially available, intravitreal injection of clindamycin has been administered off-label to treat ocular toxoplasmosis (Fernandes-Cunha *et al*., 2017). Intraocular implants are devices composed of polymers that are incorporated into drug(s). They

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are inserted into the posterior segment of the eye aiming for the delivery of controlled and prolonged therapeutic concentrations of the drug(s) directly in the pathological site and avoiding the physiological barriers of the eye. In addition, intraocular implants may not induce systemic side effects and/or toxicity, since the plasma concentration of drug(s) may not exist or may be insignificant (Da Silva *et al*., 2010). Therefore, these systems represent an effective alternative to treat posterior eye diseases, and they have been commercially explored as nonconventional medicines to treat nonposterior uveitis, diabetic macular edema, and macular edema, following retinal vein occlusion (Da Silva *et al*., 2010). However, they are not available for the treatment of ocular toxoplasmosis.

Although the ocular toxoplasmosis is the leading cause of infectious posterior uveitis in patients all over the world, inducing severe visual impairment, over the past years, the researches on the treatment of this disease have not progressed significantly, and consequently, ocular toxoplasmosis became one of the most prevalent intraocular infections for human beings (Butler *et al*., 2013).

In this review, some information concerning systemic and ocular toxoplasmosis, their clinical manifestations, and techniques to diagnose and treat them are described. Finally, the perspectives of creating innovative pharmaceutical dosage forms to eliminate the ocular toxoplasmosis are detailed. Information was collected from ScienceDirect, Scopus, Web of Science, PubMed, and SciELO databases. The following keywords were investigated: toxoplasmosis, ocular toxoplasmosis, retinochoroiditis, and congenital toxoplasmosis; and Boolean operators associated with other keywords, such as epidemiology, ocular toxoplasmosis diagnosis, ocular toxoplasmosis treatment, and ocular toxoplasmosis perspectives in treatment, were also used. In addition, systematic reviews, metaanalyses, and some case reports related to rare clinical interventions and manifestations in the last 20 years were also selected to compose this review. The same terms were used in the Portuguese language to access information on the website of the Brazilian Ministry of Health about the national policies of diagnosis and treatment of ocular toxoplasmosis.

MATERIAL AND METHODS

A search in ScienceDirect, Scopus, Web of Science, PubMed, and SciELO databases was carried out from 1999 to 2019. The following keywords were used: toxoplasmosis, ocular toxoplasmosis, toxoplasmic retinochoroiditis, and congenital toxoplasmosis. Boolean operators associated with other keywords, such as epidemiology, ocular toxoplasmosis diagnosis, ocular toxoplasmosis treatment, and ocular toxoplasmosis perspectives, regarding the treatment were also applied. Review articles, randomized clinical trials, systematic reviews, metaanalyses, and some case reports relating to clinical interventions and clinical manifestations were selected to be analyzed and described, when relevant. Moreover, the search was carried out in the Portuguese language to access the guides from the Brazilian Ministry of Health, which describe information about prevention, diagnosis, and treatment protocols of the ocular toxoplasmosis. Finally, after collecting all the scientific data on the subject, this manuscript was divided into two parts: (1) Systemic Toxoplasmosis, including the following subsections: *T. gondii*, Seroprevalence and Gene Diversity, Life Cycle and Infection, Clinical Manifestations, Diagnosis, Treatment of Gestational and Fetal Toxoplasmosis, Treatment of Congenital Toxoplasmosis, and Treatment of Systemic Toxoplasmosis in Immunocompetent and Immunocompromised Patients; and (2) Ocular Toxoplasmosis, including the following subsections: Clinical Manifestations, Diagnosis, Treatment, Challenges in the Treatment of Ocular Toxoplasmosis, Perspectives in the Treatment of Ocular Toxoplasmosis, Vaccines, Promising Drugs, and Ocular Drug Delivery Systems.

RESULTS AND DISCUSSION

Systemic toxoplasmosis

Toxoplasma gondii

The protozoan *T. gondii* is the etiological agent that causes toxoplasmosis, a zoonotic infection that spread throughout the world. The parasite was first described in 1908 by Nicolle and Mancenaux, who worked in North Africa, and by Splendore in Brazil. Its name is derived from the species of rodents from where the parasite was isolated for the first time, *Ctenodactylus gondii* (Ho-Yen, 2009; Robert-Gangneux and Dardé, 2012).

It is an obligate intracellular parasite of the Apicomplexa phylum, which includes other parasites that infect humans, such as *Plasmodium* (malaria) and *Cryptosporidium*. They belong to the Eucoccidiorida order, *Sarcocystidae* family, *Toxoplasmatinae* subfamily, and *Toxoplasma* genus. The parasite uses the felids as definitive host species. Despite this fact, the parasite presents the capacity for replication in almost all vertebrate nucleated cells (Fernandes-Cunha *et al*., 2016; Ho-Yen, 2009).

Seroprevalence and gene diversity

In Brazil, the seroprevalence is estimated to be between 20% and 90% (Dubey *et al*., 2012; Oréfice and Bahia-Oliveira, 2005). *T. gondii*'s global seroprevalence exceeds one-third of the world's population. Values may range from about 1% to 90%, depending on the country being evaluated. Particular cultural and religious practices and socioeconomic conditions are among the determinants for the variation of seroprevalence (Flegr *et al*., 2014; Pappas *et al*., 2009). In addition, the seroprevalence is higher in hot climate countries and in socioeconomic vulnerable population which has a precarious sanitary infrastructure (Flegr *et al*., 2014; Martinez *et al*., 2018).

The parasite has a high degree of genetic diversity among its lineages, and its classification was carried out through the analysis of isoenzymes and polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). Subsequently, additional PCR-RFLP markers and microsatellite analysis were carried out to identify 12 haplogroups, including the three main serotypes (Ajzenberg *et al*., 2010; Su *et al*., 2006; Weight and Carding, 2012). The high genetic variability directly affects the course of the infection, since the strains induce different responses to the cytokines, causing diverse clinical and biochemical alterations in the infected patients (Araujo and Slifer, 2003). Serotype I showed higher virulence when compared to strains of serotypes II and III (Dardé, 2008; Mercier *et al*., 2010). Additionally, considering the genetic variability of the parasite, the

possibility of reinfection by an atypical strain can occur, leading to severe damage to the patient due to the lack of immunity to that strain (Bodaghi *et al*., 2012).

Life cycle and infection

According to Robert-Gangneux and Dardé (2012) and Neves *et al*. (2009), *T. gondii* shows a complex reproductive cycle, in which the sexed phase (coccidian) occurs in felids (definitive host) and the asexual phase occurs in several warm-blooded hosts, such as birds and mammals including cats. The sexed phase occurs in the small intestine's epithelium of the felids not immune to the parasite. After ingestion and consequent infection by cysts, oocysts, or tachyzoites, a process of multiplication by merogony occurs (schizogony), originating the merozoites. They are released after the parasitized cells break into new epithelial cells; then, gametogonia are developed, initially originating the gametocytes, which after a maturation process become macrogametes (immotile female gametes) and microgametes (male gametes mobile). After complete maturation of the gametes, the macrogamete remains in the epithelium and the microgametes leave the epithelial cells to initiate the fertilization process, culminating in the formation of the zygote. The zygote develops in the epithelial cells giving rise to the oocyst, which, after a few days, breaks the epithelial cells and is released into the feces in the environment, where it undergoes a maturation process called sporogony, becoming infective.

The infective parasite has three stages or forms: tachyzoites, cystic bradyzoites, and sporozoites that are protected inside mature oocysts (Bolais *et al*., 2017). Infection of intermediate hosts occurs through the ingestion of mature oocysts (containing sporozoites) released from feces in the soil and/or into watercourses, through the ingestion of flesh from accidental hosts containing cysts, and through the ingestion of bradyzoites and/or tachyzoites released into the milk, which can be found in products that do not undergo pasteurization. In addition to the possibility of infection via food and water, there is a possibility of vertical transmission characterized by congenital toxoplasmosis and solid organ transplants. The intermediate hosts include rodents, cattle, pigs, goats, birds, and mammals, in general, among them humans (Ho-Yen, 2009; Neves *et al*., 2009; Robert-Gangneux and Dardé, 2012).

Following ingestion by the host of one of infecting forms and subsequent release into the intestine, the epithelial cells are invaded, leading to a differentiation of these infecting forms into tachyzoites, which can invade a large diversity of nucleated cells. The cellular invasion is an active process, which depends on the release of proteins in a sequential way by secretory organelles, dense granules, micronemes, and rotories as well as the parasite's motility (Flegr *et al*., 2014; Ho-Yen, 2009).

When invading the cells, tachyzoites undergo endodyogeny, guaranteeing the formation of new tachyzoites that are released by the parasitized cells. They invade new cells, promoting the dissemination of the parasite in the lymphatic system and visceral organs. The infectious process induces a robust Th1 immune response, characterized by high levels of the interferon-gamma (IFN-γ), a factor directly involved in the death of the intracellular parasite, tumor necrosis factor, responsible for increasing the microbicidal activity of macrophages, and the IFN-γ by NK cells (Cordeiro *et al*., 2017).

This immune response is responsible for quickly assuring the control and containment of the tachyzoite phase of *T. gondii*. Among the mediators released, chemokine IL-10 plays an important role, since it acts to attenuate the continuous immune response, helping in reducing the extent of tissue damage (Coppens and Joiner, 2001; Cordeiro *et al*., 2017).

The activation of the immune system leads to the elimination of the majority of tachyzoites. Then, the parasites differentiate into bradyzoites and are enclosed, to avoid their total elimination, leading to the reduction of symptoms and clinical signs of the infection. The ingestion of raw or undercooked meat by humans and the ingestion of meat from intermediate hosts by felids leads to the infection by bradyzoites cysts, which reinitiate their life cycle (Flegr *et al*., 2014; Ho-Yen, 2009; Neves *et al*., 2009; Robert-Gangneux and Dardé, 2012).

Clinical manifestations

Several clinical manifestations result from *T. gondii* infection, whose severity and/or presence of signs or symptoms depend mainly on the immunological status of the patient and the genotype of the parasite responsible for the infectious process. Immunocompetent patients tend to be asymptomatic during an acute infection, whereas infection in immunocompromised individuals may be fatal (Coppens and Joiner, 2001; Flegr *et al*., 2014; Robert-Gangneux and Dardé, 2012). It is also known that, in North American and European countries, 80% of immunocompetent individuals do not show any clinical signs during the infection, but, in South America, where higher virulence serotypes and a higher number of atypical strains are present, the occurrence of signs and symptoms tends to be apparent (Montoya and Liesenfeld, 2004; Robert-Gangneux and Dardé, 2012).

The acute infection has an incubation period lasting between 3 and 21 days and a nonspecific clinical manifestation, similar to that of influenza and mononucleosis. Infection in immunocompetent individuals tends to be asymptomatic (ranging from 25% to 80% of cases) or with mild signs and symptoms, which are mostly self-limiting by reduced parasitemia and differentiated bradyzoites capable of harboring tissue cysts. Unspecific signs and symptoms are frequently observed, such as persistent cervical lymphadenopathy, headache, fever, myasthenia, and myalgia (Ho-Yen, 2009).

However, the possibility of reactivation and the manifestation of more severe conditions in immunocompetent individuals can also occur, leading to myocarditis, commitment of the central nervous system, and retinochoroiditis, which may cause retinal detachment and cataract, among other complications that will be further discussed (Flegr *et al*., 2014; Ho-Yen, 2009).

In cases of acquired infection during pregnancy, vertical transmission can happen. Congenital toxoplasmosis is caused by tachyzoites, transposing the placental barrier and compromising fetal development, leading to intracranial calcifications, mental retardation, blindness, epilepsy, chorioretinitis, myocarditis, hydrocephalus, jaundice, purpura, and pneumonitis (Khan and Khan, 2018; Tesini, 2018). The diagnosis of congenital toxoplasmosis is complex, and it can be certainly defined after evaluating the clinical manifestations, the results obtained by serology and PCR of the amniotic fluid, and, finally, if necessary, the complementary imaging tests (Brazil, 2014b; Brazil, 2018).

In immunocompromised individuals, the risk of reactivation of the parasites and/or a newly acquired infection by a more virulent strain may lead to encephalitis, retinochoroiditis, and myocarditis, among other severe manifestations (Furuya *et al*., 2019; Rey *et al*., 2017; Soleymani *et al*., 2018).

Diagnosis

The diagnosis of toxoplasmosis is based on the evaluation of clinical findings, serological tests (ELISA, Sabin–Feldman staining, IFAT, and WB), and molecular tests (PCR). The diagnosis can also be made through histopathological and immunohistological examinations; however, these methodologies depend on a high degree of qualification for its accomplishment due to the morphological similarities observed among *T. gondii* and *Trypanosoma cruzi*, *Leishmania*, and *Cryptococcus* (Brazil, 2018; Dard *et al*., 2016).

Treatment

Gestational and fetal toxoplasmosis

During pregnancy, the objectives of the treatment of acute toxoplasmosis are to prevent the maternal–fetal transmission and to reduce the damage to the newborn, if fetal infection occurred (Brazil, 2014b; Brazil, 2018).

If a pregnant woman comes from a region of high endemicity, she should have an enzymatic IgM and IgG screening, every 2 or 3 months, to rapidly detect possible acute infections. The confirmation of the presence of IgG or IgM antibodies (notably IgM) should be followed by the administration of spiramycin at the dose of 1 g (3,000,000 IU) every 8 hours orally (Brazil, 2014b).

Spiramycin appears to reduce the occurrence of vertical transmission and it has been administered when there is a suspicion or evidence of gestational toxoplasmosis. It is recommended that the spiramycin is introduced preferentially at the first 3 weeks after acute infection, and it must be used until the end of the pregnancy. Spiramycin does not cross the placental barrier; however, it prevents or delays the passage of *T. gondii* to the fetus (Brazil, 2014b; Khan and Khan, 2018). Once the acute infection has been confirmed before the 30th week, spiramycin must be administered at a dose of 1 g (3,000,000 IU), every 8 hours orally, until the end of the pregnancy. If the infection occurs after the 30th week, it is recommended to institute the maternal triple therapy: 25 mg of pyrimethamine, 12/12 hours orally; 1,500 mg of sulfadiazine, 12/12 hours orally; 10 mg/day of folinic acid, which is essential to prevent the spinal cord aplasia caused by pyrimethamine (Table 1) (Brazil, 2014b).

When fetal infection is confirmed or highly suspected (after a positive result in the amniotic fluid or the detection of typical abnormalities on obstetric ultrasonography), the administration of sulfadiazine, pyrimethamine, and folinic acid by the mother for fetal treatment is immediately initiated (Brazil, 2014b; Brazil, 2018).

Congenital toxoplasmosis

The newborns diagnosed with congenital toxoplasmosis and the ones delivered by suspected mothers, especially those who were infected at the end of the pregnancy, should immediately receive therapy for toxoplasmosis and be monitored for the presence of signs and/or symptoms of the disease (Brazil, 2018).

The drugs currently recommended for the treatment of congenital toxoplasmosis are sulfadiazine, pyrimethamine, and folinic acid, used continuously throughout the child's first year of life. The detection of active retinochoroiditis or hyper protein or retina (protein in the cerebrospinal fluid above 1,000 mg/dl) leads to the administration of prednisone or prednisolone associated with the other drugs previously described (Table 2) (Brazil, 2014a; Brazil, 2018; Brazil, 2019). The institution of treating with the drugs previously described leads to the reduction of the late sequalae of the disease (Brazil, 2014b).

Many European services use 21- to 30-days cycles of sulfadiazine, pyrimethamine, and folinic acid alternated with 4–6 weeks of spiramycin for infected children in their first year of life. However, there is no comparative study on the efficacy of the different treatment regimens. But considering that the spiramycin does not prevent the occurrence of neurotoxoplasmosis in immunosuppressed newborns, the scheme detailed in Table 2 is recommended (Brazil, 2018).

Systemic toxoplasmosis in immunocompetent and immunocompromised patients

The first-choice regimen to treat immunocompetent and immunocompromised patients involves the administration of 500 mg of sulfadiazine 4 times daily, 25 mg of pyrimethamine once a day, and 10 mg of folinic acid once a day in patients weighing less than 60 kg. In patients weighing more than 60 kg, the therapeutic regimen consists of the use of 1,000 mg of sulfadiazine 4 times daily associated with 50 mg of pyrimethamine once a day and 10 mg of folinic acid once a day (Brazil, 2018). In the case of

Table 1. Anti-toxoplasmosis drugs used in prenatal care.

Drug	Application	PPF	Posology
Folinic acid	Toxoplasmosis Infected fetus	Tablet 15 mg	1 tablet, 1×/day (during 3 weeks followed, with pause of 3 weeks, from the time of diagnosis of fetal infection until the end of gestation)
Spiramycin	Fetal infection by toxoplasmosis	Tablet 500 mg	3 g/day (until the end of pregnancy)
Pyrimethamine	Toxoplasmosis Infected fetus	Tablet 25 mg	25 mg, 8/8 hours (3 days), followed by 25 mg, 12/12 hours (3 weeks, 3 weeks apart, until the end of gestation)
Sulfadiazine	Toxoplasmosis Infected fetus	Tablet 500 mg	500–1,000 mg, 6/6 hours

PPF: Pharmaceutical presentation forms.
Adapted from (Brazil, 2010, 2018, 2019; CDC, 2018).

Table 2. Drugs used to treat congenital toxoplasmosis in the child's first year of life.

Drug[a]	Therapeutic regimen
Sulfadiazine (500 mg tablets)	100 mg/kg/day divided into 2 daily doses, for 1 year
Pyrimethamine[b] (25 mg tablets)	1 mg/kg/day in 1 daily dose, for 2–6 months, depending on the intensity of the disease Then 1 mg/kg 3 times a week, until completing 1 year of use of the drug;
Folinic acid[b] (15 mg tablets)	10 mg given 3 times a week In the occurrence of neutropenia: if < 1,000 neutrophils/mm^3, increase the dose to 20 mg daily. if < 500 neutrophils/mm^3, use pyrimethamine until recovery occurs. Hold for another week after stopping use of pyrimethamine. Caution: folic acid should not be used in place of folinic acid.
Prednisone or Prednisolone	1 mg/kg/day in two daily doses if there is retinocoriditis in activity and/or proteinase ≥ 1,000 mg/dl. Always use in combination with sulfadiazine and pyrimethamine. Perform gradual withdrawal after process stabilization Inflammatory.
Adverse effects	Neutropenia, anemia (common), thrombocytopenia, hyperbilirubinemia, hypersensitivity reactions, gastrointestinal intolerance, crystalluria, rash.

Solutions can be produced in pharmacies with the following concentrations: Sulfadiazine 100 mg/ml; Pyrimethamine 2 mg/ml; Folinic acid 5 mg/ml (or fractionation for tablets with 5 mg each). It is recommended to carefully observe clinical jaundice and monitor bilirubin levels when sulfadiazine is used in neonates**.** Adapted from (Brazil, 2010, 2018, 2019b; CDC, 2018).
[a]Use by mouth.
[b]Drugs available only as tablets.

systemic toxicity caused by sulfadiazine, it can be replaced with dapsone associated with pyrimethamine and folinic acid or sulfamethoxazole and trimethoprim.

The alternative scheme is based on the use of 800 mg of sulfamethoxazole and 160 mg of trimethoprim twice a day or 600 mg of clindamycin thrice a day associated with 25–50 mg of pyrimethamine and 10 mg of folinic acid once a day, as well as atovaquone or azithromycin (Brazil, 2018).

However, these alternative regimens have similar rates of intolerance by the patient when compared to the first-choice scheme (Brazil, 2018; Jacobson *et al*., 2001). In addition, the recommended and alternative therapeutic regimens play a very limited role in preventing recurrences. The risk of disease recurrence is linked to the lack of efficacy of the drugs against *T. gondii* cysts (Jacobson *et al*., 2001).

After treating immunocompromised patients with the therapeutic protocols previously mentioned, HIV-positive patients with the CD4$^+$ T lymphocyte count lower than 100/µl should receive a prophylactic treatment in order to avoid reactivation, toxoplasmic retinochoroiditis, and encephalitis. Trimethoprim and sulfamethoxazole (Clotrimoxazole) are administered as drugs for prophylaxis. The suspension of the prophylactic therapy occurs when the individual has a CD4$^+$ T lymphocyte count higher than 200/µl (Ho-Yen, 2009; Kim, 2018).

Ocular toxoplasmosis

Ocular toxoplasmosis occurs due to the presence of *T. gondii* in the retina, which promotes recurrent inflammatory processes in the posterior segment of the eye named posterior uveitis (Cordeiro *et al*., 2017; Kim, 2018). In the USA, about 30%–40% of the posterior uveitis cases are caused by *T. gondii*. In central Germany, approximately 4.2% of all uveitis patients also have *T. gondii* (Jakob *et al*., 2009). In the Italian Ophthalmological Reference Center, 6.63% of uveitis cases are caused by *T. gondii* (Pivetti-Pezzi *et al*., 1996). In Brazil, 80% of the posterior uveitis cases are associated with ocular toxoplasmosis (Oréfice and Bahia-Oliveira, 2005). The majority of infected Brazilian patients develop uveitis in their second to the fourth decade of life (Holland, 2009).

The main characteristic of ocular toxoplasmosis is its recurrent character, which occurs in about two-thirds of the patients. In this case, the new lesions appear alongside the healed lesion, since dormant cysts remain at the edge of the healed lesion. Then, after a variable period of months or years, parasites differentiate into tachyzoites, leaking from the cysts, and cause a new lesion near the old scar.

The lesion begins in the retinal superficial layers and the progression of the inflammation induces damage to the deeper retinal layers and the choroid and sclera (Guex-Crosier, 2009; Scott *et al*., 2018; Tanaka *et al*., 2014). In this case, if Bruch's membrane is reached by the inflammatory process, it triggers the choroidal neovascularization frequently adjacent to the lesions. All these events may induce the damage of the peripheral vision (Neri *et al*., 2010).

Macula, fovea, and optic nerve may also be affected, which may damage the central vision (Harrell and Carvounis, 2014; Roberts and McLeod, 1999; Scott *et al*., 2018). In addition, the retinal vessels might be compromised, leading to the establishment of vasculitis, proliferative vitreoretinopathy, and traction bands, which in turn may cause secondary vitreous hemorrhage and retinal detachment. Vision loss may become permanent due to macular scar formation, optic atrophy, or retinal detachment (Kim *et al*., 2013). Finally, if the lesions extrapolate to the extraocular muscle, strabismus and convergence disorders may manifest (Kim, 2018).

Therefore, the infectious process and the vascular and ocular inflammations are potentially destructive, since they cause irreversible damage to the ocular tissues, leading to partial visual loss or blindness. The risks to vision are more significant for immunocompromised patients.

Clinical manifestations

Most cases of toxoplasmosis are asymptomatic in healthy people and the infection is self-limiting, demonstrating mild or nonexistent symptoms. However, even in these patients, during primary infection, the ocular toxoplasmosis can manifest, leading to necrotizing retinitis with secondary choroiditis, occurring adjacent to a retinochoroidal scar, and is associated with retinal

vasculitis and vitritis (Butler *et al*., 2013). In immunocompromised individuals, these events and multiple atypical presentations of ocular toxoplasmosis can manifest, increasing the risk of blindness.

In most cases, the toxoplasmic retinochoroiditis manifests unilaterally. However, in immunocompromised patients, both eyes may be damaged due to the higher probability of relapse of the disease. The lesions are satellites, multifocal, or isolated (Goldenberg *et al*., 2013).

Patients may show nonspecific clinical signs, including mild eye pain, photophobia, and blurred vision. They can also show classic manifestations, such as whitish-gray or white-gray lesions, covered by vitreous cell infiltrates. After inactivation, the lesions may have pigmented margins and a white and clear center. The healing occurs from the periphery to the center, and, despite the possibility of self-healing of the inflammatory process, the scar formation always exists, promoting visual impairment on a greater or lesser extent, depending on the location of the scar (Goldenberg *et al*., 2013).

Diagnosis

The diagnosis of ocular toxoplasmosis is based mainly on findings from the clinical examination, considering the existence of typical ocular lesions in systemic toxoplasmosis positive patients who are responsive to drug therapy. However, unresponsive patients who show atypical ocular lesions should be diagnosed by laboratory tests.

The biological diagnosis is carried out by the evaluation of the aqueous humor using the following alternatives: (1) quantitative detection of immunoglobulins by ELISA; (2) determination of the Goldmann–Witmer coefficient which represents the ratio of the value (anti-*Toxoplasma* IgG in aqueous humor/total IgG in aqueous humor)/(IgG anti-*Toxoplasma* in serum/total IgG in serum); (3) comparative qualitative analysis of IgG's serum and aqueous humor by Western Blot; and (4) analysis by PCR (Dard *et al*., 2016; Talabani *et al*., 2009).

Treatment

The therapeutic regimen to treat ocular toxoplasmosis involves the administration, for adults, of 75–100 mg of pyrimethamine, 500–1,000 mg of sulfadiazine, 2–4 times a day, and 5–10 mg of folinic acid once a day. These doses must be administered for 3 consecutive days. From the 4th day of treatment, 25–50 mg of pyrimethamine, 500–1,000 mg of sulfadiazine, 2–4 times a day, and 5–10 mg of folinic acid once a day should be used. This treatment regimen should last for 4–6 weeks (Brazil, 2010).

In the case of pregnant women, 750–1,000 mg of spiramycin should be administered every 8 hours or 600 mg of clindamycin every 6 hours. These drugs replace pyrimethamine in the first trimester of pregnancy, as it is teratogenic, and sulfadiazine in the third trimester because of the risk of the fetus developing kernicterus. Prednisone (40 mg/day) is also used for 1 week, and 20 mg/day for another 7 weeks (Brazil, 2010).

This recommended regimen must be administered orally for a prolonged period, which can cause severe side effects and toxicity. In addition to these debilitating effects, pyrimethamine and sulfadiazine are also associated with rare but potentially fatal reactions, including agranulocytosis, Stevens–Johnson syndrome, toxic epidermal necrolysis, and hepatic necrosis (Jacobson *et al*., 2001). Therefore, given the existence of side effects and toxicity of these primary therapeutic regimens, many patients discontinue the recommended treatment and opt for alternative therapeutic options, based on sulfamethoxazole, trimethoprim, atovaquone, or azithromycin (Zhang *et al*., 2018).

These drugs inhibit the multiplication of the parasites in the stage of active infection (Matias *et al*., 2014). However, they play a very limited role in preventing recurrences. The risk of recurrence is associated with the lack of efficacy of these drugs against *T. gondii* cysts (Jacobson *et al*., 2001).

Challenges in the treatment of ocular toxoplasmosis

The therapeutic regimen for the treatment of ocular toxoplasmosis varies from 4 to 6 consecutive weeks, followed by prophylaxis therapy. In cases of congenital infection, the child is treated for at least 1 year (Harrell and Carvounis, 2014; NIH, 2017). The long duration of the treatment is in part due to the resistance of the parasite in its cyst stage (Benmerzouga *et al*., 2015). According to Gajurel *et al*.'s (2016) study, *T. gondii* drug resistance is suspected to contribute to treatment failures in approximately 10% of patients during the initial therapy and in 10%–20% of patients who become intolerant during prophylaxis therapy. Finally, a study conducted in the last 10 years indicated that the parasite resistance to sulfadiazine significantly increased worldwide, including Brazil (Montazeri *et al*., 2018).

The existence of an extensive therapeutic regimen based on drugs capable of inducing significant systemic side effects and/or toxicity, the *T. gondii* resistance against the drugs administered in the therapy, and the possibility of recurrence of the ocular lesions, causing the partial or total visual loss are some of the reasons explaining the therapeutic failure of the ocular toxoplasmosis and highlight the necessity to develop new drugs and new pharmaceutical dosage forms to effectively eliminate this disease.

In order to optimize the treatment of ocular toxoplasmosis, new drugs should achieve the following characteristics: (1) physicochemical properties inducing penetration into the cysts; (2) functional organic groups inducing the elimination of bradyzoites and tachyzoites, the forms of the active parasite; (3) selectivity against parasites, avoiding the cytotoxicity of healthy cells of the host; (4) the capacity of rapidly eliminating parasites to avoid drug resistance; (5) not inducing systemic side effects and/or toxicity to the affected patient; (6) being safe to use during gestation for both pregnant woman and fetus (Garweg and Stanford, 2013). In addition, the optimization of the treatment of ocular toxoplasmosis also requires the development of new drug delivery systems capable of delivering therapeutic doses of the drug directly in the site of action for a prolonged period, minimizing/inhibiting the occurrence of systemic and/or ocular side effects and/or toxicity and *T. gondii* resistance, and improving the therapeutic efficacy of the treatment in acute and recurrent infections.

Perspectives in the treatment of ocular toxoplasmosis

Vaccines

Rezaei *et al*. (2019) screened the antigens expressed in the three infectious stages of the parasite (MIC3, MIC4, MIC13, ROP2, RON5, GRA1, GRA6, GRA8, and GRA14). These researchers also selected promising antigens found only in tachyzoites and bradyzoites (MIC1, MIC5, ROP5, ROP8, ROP16, ROP17, ROP19, ROP38, ROP48, RON4, ROM4, GRA2, GRA4, GRA10, GRA12, GRA15, GRA16, SAG3, and SAG 5A). The selected antigens are highly immunogenic and may be candidates in immunization studies for the development of an effective vaccine. It is of utmost importance that immunization studies be carried out in order to develop a vaccine not only for humans but also for felids.

Promising drugs

Over the last decade, significant progress has been made to identify and develop new compounds for the treatment of toxoplasmosis and/or ocular toxoplasmosis. These compounds should be optimized to obtain maximum efficacy against *T. gondii* (Jones *et al*., 2016; Sugden *et al*., 2016). These substances were described in Table 3.

Ocular drug delivery systems

To overcome the drawbacks of conventional pharmaceutical dosage forms, new therapeutic alternatives have been developed and explored to extinguish the infectious lesions and the inflammatory process generated by ocular toxoplasmosis (Matet *et al*., 2019; Streilein, 2003). However, the researches based on the treatment of this disease are not numerous.

Tennikova and Urtti (2018) showed drug transport systems based on modified cells as a promising possibility of treating ocular diseases, including the toxoplasmic retinochoroiditis. They would be capable of assertively directing the drug to the site of action and releasing and prolonging its retention. However, further studies are necessary to evaluate the biocompatibility and safety of these modified cells. In addition, production, sterilization, storage, and transportation processes still require improvements for scaling up.

Tamaddon *et al*. (2015) developed poly(L,D-lactic acid) (PLA)-based biodegradable clindamycin phosphate implants for the treatment of ocular toxoplasmosis. These intravitreal implants were prepared by the melt extrusion method, and they are rod-shaped with a length of 5 mm and a diameter of 0.04 mm. They are characterized by different analytical techniques, which demonstrate that the manufacturing process did not induce any chemical or physical modifications either on the drug or on the polymeric matrix. This study indicated the viability in producing PLA implants loaded with clindamycin phosphate to treat ocular toxoplasmosis. However, preclinical and clinical trials should be carried out to evaluate the *in vivo* performance of these implants.

Fernandes-Cunha *et al*. (2017) developed intravitreal poly(lactic-co-glycolic acid) (PLGA) implants containing clindamycin hydrochloride to treat ocular toxoplasmosis. These implants were revealed to be safe *in vitro* and *in vivo* against delicate ocular cells. They did not promote modifications in the morphology of human retinal pigment epithelial cells *in vitro* since their actin filaments and nuclei were completely preserved after direct contact with the implants. In addition, after 30 days in the vitreous cavity of mice eyes, the implants did not induce any retinal morphological alterations, and the photoreceptors from retinal layers were completely organized, confirming the inexistence of activation of cell death by apoptosis. These results demonstrated the safety of clindamycin hydrochloride-loaded PLGA implants and indicated that these devices may be applied in the treatment of ocular toxoplasmosis.

Micro intraocular implants intended for the treatment of ocular toxoplasmosis (Patent BR 10 2017 019794 8) described the development of microimplants composed of PLGA and spiramycin, an anti-*Toxoplasma* and anti-inflammatory drug. These small implants (2.78–3.22 mm in length) can be inserted in the vitreous cavity to simultaneously treat infection caused by *T. gondii* and inflammation when ocular toxoplasmosis is established. In addition, these microimplants may not induce damage to the delicate ocular tissues or increase the intraocular pressure after their insertion due to the reduced size (Silva and Tavares, 2017).

Peyman *et al*. (1988) injected intravitreal liposome-encapsulated clindamycin in a patient with acute toxoplasmosis

Table 3. Potential drugs for the treatment of toxoplasmosis and/or ocular toxoplasmosis.

Class or promising compound	Authors
Artemisinin derivatives (CPH4-136 and LEW3-27)	Schultz *et al*., 2014
Bis phosphonate compounds (Alendronate, Risedronate)	Yardley *et al*., 2002
Protein Kinase Inhibitors (Potent Inhibitors of TgCDPK1)	Vidadala *et al*., 2016
Dihydro folate reductase inhibitors – DHFR (Dihydrotriazines)	Mui *et al*., 2008
Inhibitors of fatty acid synthesis (Triclosan and derivatives)	Muench *et al*., 2013
Inhibitor of β –ketoacylacetyl (Tiolactomycin)	Martins-Duarte *et al*., 2009
Fluoroquinolones derivatives	Dubar *et al*., 2011
Inhibitors of acetyltransferases – HAT (L-arcinol)	Jeffers *et al*., 2016
Ruthenium-based complexes	Barna *et al*., 2013
Niclosamide derivatives (Salicylanilides)	Fomovska *et al*., 2012
Spiroindolone (NITD609)	Rottmann *et al*., 2010
Spiroindolone (NITD609)	Gwilt and Tracewell, 1998
Anticoccidiary Triazine (toltrazuril)	Streilein, 2003

retinochoroiditis. Five weeks after injection, the parameters from electroretinography showed improvement consistent with the clinical evolution in the inflammatory lesion. After 6 weeks, the inflammation was completely resolved, and the visual acuity of the patient improved. Liposomes may be a therapeutic alternative to treat ocular toxoplasmosis.

In conclusion, ocular toxoplasmosis is an infectious and inflammatory disease that induces toxoplasmic retinochoroiditis. It has a destructive potential since it causes the reduction of visual acuity or blindness. The diagnosis of ocular toxoplasmosis is based on the clinical manifestations and laboratory analyses, and the treatment is based on the oral and intravitreal administrations of antibiotic and corticosteroid drugs. However, these drugs may induce systemic side effects and/or toxicity, reducing the compliance of the patients to therapy. In addition, *T. gondii* resistance to these drugs threatens the healing potential of the available drugs. Considering this scenario, new active principles, vaccines, and pharmaceutical dosage forms should be developed to improve the possibility of healing the ocular toxoplasmosis and, consequently, limit vision loss. Among these pharmaceutical dosage forms under development, the polymeric implants containing clindamycin and spiramycin should be mentioned, as they can deliver therapeutic doses of drugs directly in the vitreous cavity of the affected eye. In addition, the prolonged delivery of drugs from these implantable devices may effectively act against parasites in active and cysticidal forms, preventing disease recurrence and *T. gondii* resistance. However, in addition to the existence of these new therapeutic alternatives, the implants have not been evaluated clinically, constituting only a perspective for locally treating ocular toxoplasmosis.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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