Treatment Modalities of Toxoplasmosis

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Abstract

Primary *Toxoplasma gondii* infection is usually subclinical, but cervical lymphadenopathy or ocular disease can be present in some patients. Active infection is characterized by tachyzoites, while tissue cysts characterize latent disease. Infection in the fetus and in immunocompromised patients can cause devastating disease. The combination of pyrimethamine and sulfadiazine (pyr-sulf), targeting the active stage of the infection, is the current gold standard for treating toxoplasmosis, but failure rates remain significant. Although other regimens are available, including pyrimethamine in combination with clindamycin, atovaquone, clarithromycin, or azithromycin or monotherapy with trimethoprim-sulfamethoxazole (TMP-SMX) or atovaquone, none have been found to be superior to pyr-sulf, and no regimen is active against the latent stage of the infection. Furthermore, the efficacy of these regimens against ocular disease remains uncertain. In multiple studies, systematic screening for Toxoplasma infection during gestation, followed by treatment with spiramycin for acute maternal infections and with pyr-sulf for those with established fetal infection, has been shown to be effective at preventing vertical transmission and minimizing the severity of congenital toxoplasmosis (CT). Despite significant progress in treating human disease, there is a strong impetus to develop novel therapeutics for both the acute and latent forms of the infection. Here we present an overview of toxoplasmosis treatment in humans and in animal models. Additional research is needed to identify novel drugs by use of innovative high-throughput screening technologies and to improve experimental models to reflect human disease. Such advances will pave the way for lead candidates to be tested in thoroughly designed clinical trials in defined patient populations.

Keywords: Toxoplasmosis, Treatment

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Introduction:

Toxoplasma gondii is an intracellular pathogen affecting approximately one-third of the human population. It exists in nature as oocysts, bradzyzoites (contained in latent tissue cysts), and replicating tachyzoites, with the last form being the hallmark of active disease. Human infection is acquired via ingesting food or water contaminated with sporulated oocysts or undercooked meat infected with latent cysts, by mother-to-child transmission, or via an infected allograft during organ transplantation. Acquisition via blood products or by accidental ingestion or inoculation of *Toxoplasma* in laboratories working with the parasite is rare. Acute infection is typically asymptomatic in immunocompetent individuals, but cervical lymphadenopathy or ocular disease can occur. Infection of immunocompetent individuals with more virulent strains of *T. gondii*, which are prevalent in Latin America, can result in severe pneumonia and disseminated disease, including death. In pregnant women, acute infection acquired during or shortly before gestation can lead to congenital toxoplasmosis (CT) even though the mother remains asymptomatic. Acute infection in the immunocompetent host is followed by asymptomatic latent infection, during which the parasite encysts in various organs, especially the cardiac and skeletal muscles, brain parenchyma, and retina. Latent infection can reactivate overtly in immunocompromised patients, with conversion of latent bradyzoites into rapidly replicating tachyzoites, causing severe, life-threatening disease with significant morbidity and 100% mortality if left untreated. Latent infection can also reactivate locally in the retinas of immunocompetent individuals, leading to significant loss of visual acuity and economic productivity. (**Hajj *et al.,*2021)**

Treatment of toxoplasmosis:

General anti-parasitic and antibacterial drugs which are used for treatment of toxoplasmosis remain limited and therapeutic strategies for this disease vary regarding to the state of the disease and the host immune response (**Hajj *et al.,*2021)**

Pyrimethamine and sulfadiazine:

Pyrimethamine is an inhibitor of dihydrofolate reductase (DHFR) enzyme which blocks purines and pyrimidines synthesis. Sulfadiazine is an inhibitor of dihydropteroate synthase (DHPS). Both these drugs are commonly used as combination **(Silva *et al.,*2019).** As *T. gondii* synthesizes folates denovo **(Blume and Seeber, 2018)**, these combined drugs exhibit its anti-parasitic action via blocking the parasitic biosynthesis of the folates, hence interrupting nucleic acid synthesis and parasite replication **(Dunay *et al.,*2018).**

However, usage of this combination leads to bone marrow myelosuppression , this harmful side effect may be reduced by the administration of pyrimethamine and sulfadiazine with the folinic acid (leucovorin) which is considerd as active folic acid metabolite and crucial co-enzyme for nucleic acid synthesis (**Alday and Doggett, 2017).** In addition, neutropenia, leukopenia, thrombocytopenia, and teratogenic effect occur if the drugs were introduced during the first trimester of pregnancy and rarely, toxic epidermal necrolysis, agranulocytosis and hepatic necrosis may be occurred **(Shammaa *et al.,*2021).**

pyrimethamine is given in a dose of 25 mg/day by the oral route for 3-4 weeks in adults and 2 mg/kg/day for 3 days (to a maximum daily dose of 25mg) and 1 mg/kg/day for 4 weeks in children. Whereas the dose of sulphadiazine is 4-6 gm/day for 3-4 weeks in adult and100-200 mg/kg/day for 3-4 weeks in children **(Alvarado *et al.,* 2011).**

Clindamycin

Clindamycin is a lincomsamide antibiotic that is often used in combination with sulfadiazine for the therapy of toxoplasmic retinochoroiditis and encephalitis, especially in patients allergic to sulphonamides **(Fichera *et al.,* 1995).** Clindamycin (at a dose of 2.4-4.8 gm/day) can be substituted if severe sulphonamide toxicity occurred **(Cook and Zumulla, 2003).**

Atovaquone:

Atovaquone is a hydroxy-1, 4-naphtoquinone antibiotic. It is a safe and effective treatment against tachyzoites and cyst forms of *Toxoplasma* **(Reis *et al.,* 2015).**

Atovaquone acts by targeting mitochondrial respiration to block and collapse the membrane in the organisms **(Freyre *et al.,* 2008).** Atovaquone has been shown to protect against maternal and congenital toxoplasmosis as well as inflammatory complications in animal model **(OZ, 2014).** Atovaquone can be used as an alternative in patients who are unable to tolerate either sulfonamides or clindamycin **(Halonen and Weiss, 2013).**

Spiramycin:

Spiramycin is produced by *Streptomyces ambofaciens* and contains three 16-membered-ring macrolide antiparasitic and antibiotic **(Rubinstein and Keller 1998).** It is used in the treatment of toxoplasmosis **(Engel *et al.,* 2000)** and cryptosporidiosis (**Perng *et al.*, 2003).** It is also used in the treatment of different soft tissues infections, urinary and reproductive systems infection **(Mourier and Brun 1997)** as well as digestive and respiratory systems infection **(Bunetel *et al.,* 2001).**

The exact mechanism of action of spiramycin on toxoplasmosis is not well clarified. However, its action can be explained as it inhibits protein synthesis. **(McCarthy *et al,* 2014).** Spiramycin is used broadly in Europe. It is exclusively used to prevent maternal-fetal transmission of the organism. However, spiramycin monotherapy is less effective than pyrimethamine or sulfadiazine **(Gilbert and Gras, 2003).**

Spiramycin is highly concentrated in tissues especially, in the placenta. It can be given to pregnant women who are primarily infected with *Toxoplasma* without teratogenic effects to the fetus. Spiramycin should be given at a dose of (3 gm/day) throughout the pregnancy to reduce risk of transplacental passage of the parasite **(Cook and Zumulla, 2003).**

It is often used for treatment while waiting for diagnostic testing for prenatal transmission. In some studies, it is continued for women in whom acute toxoplasmosis is documented even if tests for prenatal transmission are negative **(McLeod *et al.,* 2009).**

Spiramycin has good bioavailability, ranging from 30% to 40%. Administration away from meals is recommended because food reduces bioavailability by 50% and delays the time-to-peak serum concentration **(McCarthy *et al,* 2014)**

Side effects of spiramycin are rare, they include pseudomembranous colitis, cholestatic hepatitis **(Saab and Mroueh, 2002),** QT segment prolongation with dysrhythmia **(Stramba-Badiale *et al.,* 1997),** thrombocytopenia and oxidative hemolysis in glucose-6-phosphate dehydrogenase–deficient patients. Excretion is predominantly through the biliary route, with some enterohepatic recirculation. The drug is relatively free of significant drug interactions **(McCarthy *et al.,* 2014).**

Other agents:

Other agents with therapeutic effect against *T. gondii* include azithromycin, clarithromycin, dapsone, minocycline, rifabutin and roxithromycin **(Montoya and Remington, 2000)**. Anti-*T .gondii* agents act on metabolically active stages i.e "tachyzoites". They are effective in controlling disease in acute infections by eliminating tachyzoites. Tissue cysts and bradyzoites are not metabolically active stages but latent stages with minimal metabolic activity. Currently, no chemotherapeutic agent has been identified that kills or eliminates *T. gondii* tissue cysts and bradyzoites **(Peng *et al.,* 2015).**

Treatment of acquired toxoplasmosis:

Many of these infections are self-limited and resolve without specific treatment or with symptomatic management (i.e. ibuprofen for pain and fever). Treatment with pyrimethamine and sulfadiazine for 4 weeks is effective and is used for moderate to severe cases **(Halonen and Weiss, 2013).**

Treatment of congenital toxoplasmosis (CT):

There are two reasons for the introduction of particular anti-*T. gondii* medication: (1) prenatal treatment to stop materno-fetal parasite transmission (MFTP) and/or lessen foetal harm, and (2) postnatal treatment to reduce clinical symptoms and/or stop long-term effects in the infected newborn **(Robert-Gangneux, 2014).**

However, due to complicating circumstances, the literature's appreciation of the advantages of prenatal care has varied**,** because it could depend on a variety of factors, including the type of treatment, when it is introduced after maternal infection, the dosage plans, and the length of time. Knowing the precise timing of maternal infection is thus necessary and only possible in nations with prenatal serological screening programmes, i.e. a small number of European nations. Particularly in asymptomatic or subclinically infected patients, for whom the length of treatment and the long-term advantages are still being debated, the benefit/risk ratio of postnatal treatment has also been questioned **(Petersen, 2007).**

- Prenatal treatment:

Spiramycin (SPI), is typically prescribed to infected women during pregnancy (or close to conception) and is considered an excellent first-line treatment for the prevention of MFTP because it a strong macrolide antibiotic that accumulates in the placenta **(Dunay *et al.,* 2018).**

SPI is a comfortable treatment choice while waiting for amniocentesis because of the minimal incidence of side effects. Unfortunately, because SPI barely passes the placental barrier, it is ineffective for treating a foetal infection that has already developed **(Robert-Gangneux *et al.,* 2011).**

PCR analysis of the AF samples from the 16th gestational week (gw) onwards allows for a treatment switch to PYR-based combinations, primarily PYR – sulfadiazine combination (PYR-SDZ) when a positive PCR result is obtained. However, the PYR-SDZ combination is teratogenic and hence should be avoided during the first 14 gw, although this cut-off varies between countries **(Dunay *et al.,* 2018).** Anyway, prenatal diagnosis is never performed before 14 gw, thus SPI treatment is the rule during the first trimester of gestation **(Konstantinovic *et al.,* 2019).**

- Postnatal treatment:

When congenital infection is diagnosed, postnatal treatment is initiated with the goal of preventing or minimising clinical symptoms at birth and easing potential long-term sequelae or clinical relapses, primarily eye sequelae **(Konstantinovic *et al.,* 2019).**

The 1994 Chicago Collaborative Treatment Trial (CCTT), a landmark study that altered the general approach to post-natal treatment of CT, showed a promising result of a year-long PYR-SDZ treatment in 120 infected neonates followed up between 1981 and 2004, significantly better than in untreated (or sub-optimally treated) historical controls. Even among infants with significant birth defects, 80% had adequate motor function, 64% lacked new eye abnormalities, and none lost their sensorineural hearing **(McLeod McLeod *et al.,* 2006).**

Congenitally infected children should receive PYR-SDZ medication consistently throughout the duration of their first year of life, according to actualized recommendations recently issued by **Maldonado, Read, and the Committee on Infectious Diseases (CCTT, 2017).**

Treatment of Cerebral Toxoplasmosis:

Since Toxoplasmic Encephalitis (TE) is the most prevalent clinical symptom seen in a large percentage of HIV-infected individuals, the disease's spectrum has shifted as non-HIV immunocompromised patients have become more prevalent **(Robert-Gangneux *et al.,* 2015).** In fact, the prognosis is worse in non-HIV patients, and toxoplasmosis spreads more frequently than it does within the CNS. Patients who have undergone a bone marrow or hematopoietic stem cell transplant (HSCT) are particularly at risk since, despite treatment, death rates range from 38% to 67%. **(Gajurel *et al.,* 2015).** Therefore, curative toxoplasmosis treatments must penetrate the blood brain barrier and be highly and swiftly successful **(Konstantinovic *et al.*, 2019).**

The treatment of toxoplasmic encephalitis requires combination of: sulfadiazine 1000 mg four times a day (or 1500 mg four times a day if weight is more than 60 kg) and pyrimethamine 200 mg loading dose followed by 50 mg of pyrimethamine daily (or 75 mg daily if weight if more than 60 kg) **(Kaplan *et al.,* 2009).**

Leucovorin (folinic acid) 10 mg daily is given to prevent hematological toxicity. If sulfadiazine is not tolerated, it may be replaced by clindamycin 600 mg four times a day. Alternative regimens based variously on trimethoprim and sulfamethoxazole combination, atovaquone and dapsone have been reported **(Dedicoat and Livesley, 2006).**

Steroids may be useful in cases with significant cerebral edema. Neurological imaging should be done 2 weeks after initiating therapy to assess efficacy of treatment **(Halonen and Weiss, 2013).**

In AIDS patients with toxoplasmosis, treatment includes acute therapy which comprises sulphadiazine (4-8 gm/day). Pyrimethamine (50-75 gm/day) with vitamin supplements continued for 6 weeks **(Cook and Zumulla, 2003).**

Treatment of Ocular toxoplasmosis:

Treatment of ocular toxoplasmosis depends on several factors including the location of lesions, degree of inflammation, the threat of blindness and immune status of the patient **(Yuliawati and Nasronudin, 2015).**

If the infection is not on the optic disc and macula and is only accompanied by mild inflammation, treatment is not required **(Mechain *et al.,*2000).**

Pyrimethamine and sulfadiazine as well as Trimethoprim/ sulfamethoxazole have been effective therapeutic agents. Systemic steroids can be added to avoid further damage of the retina by the inflammation. Treatment needs to be started before necrosis and damage to the retina occurs, which is caused by recurrent bouts of the retinochoroiditis **(Phan *et al.,* 2008).**

Drug Resistance in *Toxoplasma gondii* infections:

The rise of resistant strains was described in addition to the lack of the usual anti toxoplasmic therapeutic medicines and several reported bad effects for the already prescribed medication **(Montazeri *et al.,*2018**).

This resistance may be a contributing factor in individuals with acute toxoplasmosis or those who relapse during suppressive therapy failing to respond to treatment. The degree to which this medication resistance results in treatment failure cannot be easily evaluated because of the difficult recovery of *T. gondii* from infected individuals **(Alday and Doggett, 2017).** Despite this, changes in the common enzyme targets of the folate pathway, dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS), were discovered **(Doliwa *et al.,* 2013).**

In that regard, several DHPS gene polymorphisms were found in a Brazilian isolate of infant sulfadiazine-resistant congenital toxoplasmosis. However, no association was seen between any known DHPS polymorphisms and the susceptibility profile to sulfadiazine **(Silva *et al.,* 2017).**

Clinical isolates of the atypical RMS-2001-MAU strain, type I B1 strain, and type II RMS-1995-ABE strain all shown sulfadiazine resistance **(Meneceur *et al.,*2008).** One of 31 proteins that were found to be differentially regulated between sulfadiazine sensitive and resistant strains using a proteomic approach was the rhoptry protein ROP2A virulence factor, which was significantly abundant in two naturally resistant Type II strains of *T. gondii,* TgH32045 and TgH32006 **(Doliwa *et al.,*2013).**

Therapeutic failure of toxoplasmosis has been reported especially in cases of immunocompromised individuals as well as congenital transmission. These therapeutic failures followed by the development of drug-resistant parasites may be associated with host factors such as malabsorption or intolerance of the drug and/or parasitic factors such as variability in drug susceptibility between genetically different parasite strains **(Meneceur *et al.,* 2008).**

Owing to drug resistance, researchers switched their attention recently to parasitophorous major surface antigens, namely SAG1, *T. gondii* dense granule antigen (GRA) 4 and GRA 7, and *T. gondii* rhoptry protein (ROP) 2 as innovative and suitable candidates for the development of a vaccine against toxoplasmosis **(Garcia *et al.,* 2014).**

Atovaquone resistance:

Atovaquone is a substituted hydroxynaphthoquinone compound that is being used clinically for the treatment of *T. gondii* infections against chronic bradyzoite stage via mitochondrial electron transport chain inhibition **(Tomavo and Boothroyd, 1995).**

Cytochrome bc1 complex (CYT bc1) is a membrane-bound enzyme of the respiratory electron transfer chain located in the inner mitochondrial membrane. It is a successful drug target for *T. gondii* **(Lawres *et al.,* 2016).** CYT bc1 reduces cytochrome c and generates an electrochemical gradient by transferring protons to the intermembrane space. It also creates ubiquinone for pyrimidine biosynthesis. CYT bc1 has two active sites, the bc1 Qo site (oxidizes ubiquinol) and the bc1 Qi site (reduces ubiquinone) **(Crofts, 2004).** The genetic evidence revealed that atovaquone, targets *T. gondii* CYT bc1 by binding to Qo domain of cytochrome b confer resistance to atovaquone **(McFadden *et al.,* 2001).**

Mutants of *T. gondii* resistant to clindamycin, spiramycin, and azithromycin:

Antibiotics such as clindamycin, spiramycin, and azithromycin are known to be active against *T. gondii*. However, mutant ClnR -2 (RH) was cross-resistant to clindamycin, azithromycin, and spiramycin antibiotics **(Pfefferkorn and Borotz, 1994).** Interestingly, resistance to these drugs is encoded in the rRNA genes of the 35-kb genome in *T. gondii* and the apicoplast protein synthesis is known as target of these antibiotics action against *T. gondii* **(McFadden *et al.,* 2001).**

Recently the drug resistance in *Toxoplasma* is ongoing and the emergence of *T. gondii* strains resistant to current drugs represents a concern not only for treatment failure but also for increased clinical severity in immunocompromised patients.

Thus, understanding mechanisms of drug resistance is essential for controlling the disease and it helps identify targets that are crucial to the parasite and predicts which combinations of drugs should act synergistically. Also, establishing a more effective therapeutic scheme in the treatment of toxoplasmosis, particularly among high-risk individuals is critically needed. Additionally, monitoring the presence of resistant parasites, particularly in food products, would thus seem a prudent public health measure. Further development of a greater understanding of exact mechanisms of drug resistance in *T. gondii* is needed to improve the therapeutic outcomes in patients **(Montazeri *et al.,*2018).**

Prevention and control of toxoplasmosis:

The consumption of undercooked meat containing viable tissue cysts is the major route of infection in most parts of the world. In regions with poor water hygiene, ingestion of oocyst-contaminated soil and water, or contact with infective oocysts, are other important sources of infection. Infection with oocysts has become an increasingly important source of infection **(Pereira *et al.,* 2010).**

Moreover, prevention of exposure to tissue cysts begins at the initial handling of raw meat that is potentially infected. Individuals handling meat should wash their hands thoroughly with soap and water before they go to other tasks in the kitchen. Tissue cysts and bradyzoites from meat that has been cut or chopped with knives or other utensils can contaminate cutting boards; sink tops or knives, leading to accidental ingestion by food workers. *T. gondii* tissue cysts in meat are to be killed by exposure to extreme cold or heat. They are killed by heating meat throughout to 67◦C or by cooling meat to −13◦C **(Dubey, 2010).**

In fact, *Toxoplasma gondii* oocysts can survive for years in the environment. The absence of cats does not mean an absence of oocysts in the environment. Gloves should be worn while gardening to prevent exposure to oocysts in the soil. Vegetables should be washed thoroughly before eating because they may have been grown in or harvested from soil contaminated with oocysts or irrigated with water containing oocysts **(peng *et al.,* 2015).**

There is minimal danger of acquiring *T. gondii* infection by drinking cow's milk from commercial sources because it is generally pasteurized. Consumption of non-pasteurized goat's milk has been indicated as a potential cause of congenital, ocular and acute toxoplasmosis **(Walsh *et al.,* 1999).**

It is also recommended to keep cats indoors, feed them commercially prepared diets and clean their litter boxes daily. It takes at least one day for the organisms to sporulate and become infectious after being shed **(Vollaire *et al.,* 2005).**

Recommendations specifically for pregnant women include wearing gloves when gardening or being in contact with soil or sand, followed by thorough handwashing **(Mitchell *et al.,* 2006).** In addition, pregnant women should avoid changing cat litter if possible **(Lopez *et al.,* 2000).**

Early detection with repeated serological examination and the treatment of pregnant women can reduce the risk of infection by *T. gondii* **(Chintapalli and Padmaja, 2013).** Serum monitoring throughout pregnancy, to detect early maternal seroconversion **(Lopes -Mori *et al.,* 2013).**

A lack or incomplete prenatal treatment was identified as an important risk factor for congenital toxoplasmosis, reinforcing the need of improvement of prenatal care **(Campello Porto and Duarte, 2012).**

Universal prenatal screening procedures have been adopted. In France, for example, screening of pregnant women, in utero diagnosis and treatment are routinely performed **(Garcia-Meric *et al.,* 2010)**. Routine prenatal treatment has been advocated given the suggested improved clinical outcome in reducing transplacental transmission (**McLeod *et al.,* 2009).**

***Toxoplasma* vaccination:**

Vaccines are prepared against infectious disease agents utilizing a variety of immunization strategies and delivery platforms. These include using whole disease-causing microorganisms, some of their components or genetic modification by the process of weakening living organisms through cultivation (live-attenuated vaccine). Vaccines may be also produced through the process of inactivating whole organisms by chemicals, heat treatment or other means (inactivated vaccine) **(Karch and Burkhard, 2016).**

Vaccination against viral and bacterial pathogens is a widespread, routine, and successful practice; however, to date none is successful against a protozoan pathogen of humans **(Hajissa *et al.,* 2019).**

Vaccines prepared from *T. gondii* stage-specific antigens are thought to be pivotal to stage-specific protection. Leading modern vaccine design strategies for *T. gondii* include epitope mapping to design multi-epitope vaccines, live-attenuated vectors as vehicles for delivery and expression of an antigen, and heterologous prime boost regimens **(Foroutan *et al.,* 2019).**

A very large number of around 1,360 protein families have been described as potential targets to develop a vaccine against *T. gondii* infection. Among these, surface antigen glycoproteins are considered crucial to host cell attachment and host immune evasion **(Garcia *et al.,* 2014).**

Activation of protein-coding genes including TLR4 and TLR5 that trigger human T cells to prevent toxoplasmosis could be a promising vaccine strategy **(El Bissati *et al.,* 2017).**

For more than two decades efforts have been made to develop a vaccine against *T. gondii* in animals to reduce oocyst shedding in cats and tissue cyst formation in mammals. Nevertheless, so far only a live-attenuated vaccine based on the S48 strain has been licensed for veterinary use **(Zhang *et al.,* 2013).**

In a concerted drive to find a *T. gondii* vaccine, more than one hundred experimental studies were reported for the five-year period 2009-2013. In 78.0% of these investigations a mouse model was exploited, followed by sheep and pigsin 5.5 and 1.8% of studies, respectively **(Garcia *et al.,* 2014).**

Superoxide dismutase produced by *T. gondii* is very important for bradyzoite and tachyzoite stages to grow within host cells. A mouse model study revealed that a vaccine developed from *T. gondii* DNA elicited strong parasite-specific humoral and cellular immune responses, so superoxide

dismutase has been suggested as a potential candidate for future *T. gondii* vaccine development **(Zhang *et al.,* 2019).**

Considering the role of rhoptry antigens in virulence and satisfactory immunogenicity, they could be promising vaccine candidates against *T. gondii* **(Liu *et al.,* 2012).**

Toxovax is the only accepted vaccine against toxoplasmosis which contains live attenuated S48 strain that controls congenital infection in ewes **(Black and Boothroyd, 2000).** Toxovax decreases the abortion rate but does not eradicate the parasite completely. However, it is expensive and may be changed into a pathogenic form; so, it is not suitable for human use **(Kur *et al.,* 2009)**

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