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Congenital Toxoplasmosis: Time for a New Treatment Approach

Sam D Chorlton*

Department of Pathology and Laboratory Medicine, University of British Columbia, Canada

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***Corresponding author:** Sam D Chorlton, Faculty of Medicine, Rm. G227–2211 Wesbrook Mall, Vancouver, BC Canada V6T 2B5, Canada, Tel: 1-289-983-5997; Email: sam.chorlton@medportal.ca

Abstract

Congenital toxoplasmosis is caused by in utero infection of the fetus with the intracellular parasite Toxoplasma gondii. Upon infection, the parasite forms life-long cysts in fetal brain which are resistant to the currently accepted therapy of pyrimethamine and sulfadiazine. These cysts commonly reactivate later in life causing visual impairment through chorioretinitis, and less frequently neurological impairment such as hydrocephalus, cortical atrophy, seizures and encephalopathy. New therapies have the potential to alleviate a significant burden of disease by reducing cyst burden in neonatal brain. Atovaquone is perhaps the most promising drug given its low side-effect profile, established safety and efficacy in animal models. Randomized trials are needed to evaluate it and other potential drugs as adjunctive treatment in congenital toxoplasmosis.

Keywords: Congenital toxoplasmosis; Toxoplasma gondii treatment; Chorioretinitis; Atovaquone

Abbreviations: CSF: Cerebrospinal Fluid; T. Gondii: Toxoplasma Gondii; G6PD: Glucose-6-Phosphate Dehydrogenase; FDA: Food & Drug Administration; HIV: Human Immunodeficiency Virus; WHO: World Health Organization

Introduction

Congenital toxoplasmosis continues to exact a significant toll on infected infants, despite lengthy and complicated treatment. Between 1 in 1000 and 1 in 10,000 infants are affected with the disease depending on geographical region [1,2] and clinical presentation of the disease ranges from asymptomatic to severe neurological impairment and death. At birth, a majority of infected neonates are asymptomatic; affected neonates can present with chorioretinitis, abnormal CSF, seizures, intracranial calcifications and more. Both asymptomatic and symptomatic treated infants are at risk for late ophthalmologic and Neuro developmental complications such as hydrocephalus, cortical atrophy, seizures and encephalopathy. In a prospective study of 477 infants treated with standard therapy and followed for a median of 10.5 years, the cumulative probability of new retinal lesions was 50% by 18 years of age and 9 infants developed new severe neurologic deficits [3].

Congenital toxoplasmosis is caused by vertical infection of the fetus with the intracellular parasite Toxoplasma gondii. Transmission almost always occurs during primary infection of the mother via exposure to contaminated soil or water, or undercooked meat [4]. The time of maternal infection is correlated with the risk of vertical transmission (15% at 13 weeks gestational age vs. 71% at 36 weeks) and inversely correlated with severity of complications [5]. In acute infection, T. gondii tissue cysts, containing the bradyzoite form of the parasite, or oocysts, containing the sporozoite form of the parasite, convert into tachyzoites in maternal gastrointestinal epithelium and enter her blood. These tachyzoites are fast replicating and cross the placenta to invade fetal neural tissues. Starting as early as 7 days after infection of the fetal brain, tachyzoites convert back into bradyzoites and form life-long tissue cysts [6].

Postnatal treatment guidelines for congenital toxoplasmosis suggest a combination of pyrimethamine, sulfadiazine and folinic acid for one year [7]. This recommendation is based on expert opinion [8] and observational studies showing a lower incidence of long term complications compared with shorter treatment in historical controls [9,10] although there are significant risks of treatment including bone marrow suppression, neutropenia, thrombocytopenia, megaloblastic anemia, allergic reaction and renal failure. More importantly, however, is the lack of activity of these drugs against the bradyzoite stage of the T. gondii. Periodically and for unknown reasons, bradyzoites reactivate

causing overt disease and the aforementioned late complications of congenital toxoplasmosis. In fact, pyrimethamine and sulfadiazine therapy may enhance conversion of tachyzoites into bradyzoites as they represent a form of cellular stress [11,12]. Without a reduction of cyst burden in the neonatal brain, there is little hope for prevention of long term complications of the disease.

Conclusion

Given the high rate of disease reactivation in infants treated for congenital toxoplasmosis, new treatment approaches have the potential to ameliorate a significant burden of disease. At the time of writing (July 2017), there are four and two trials registered in ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform, respectively, with keywords 'congenital toxoplasmosis'; none of these trials examine novel anti parasitic agents. Two recent reviews highlight currently approved and investigational drugs with activity against different stages of Toxoplasma [13,14]. Future research should examine agents with demonstrable activity against the chronic, bradyzoite stage of T. gondii. Notably, animal studies have demonstrated activity of spiramycin combined with metronidazole [15] didanosine [16], miltefosine [17], itraconazole [18], and atovaquone [19-22] with or without clindamycin [23] against chronic toxo plasma infection in vivo. Some of these agents are established and safe in pediatrics.

Atovaqu one is perhaps the most promising given its low side effect profile [24], selective anti parasitic activity [25], single drug administration, lack of interaction with standard therapy, and FDA approval for other pediatric disease (ie malaria with proguanil) [26]. Atovaquone has already been successfully used for acute toxoplasmosis in adults, either in combination with pyrimethamine and folinic acid, or with sulfadiazine, or as a single agent [27]. In two uncontrolled trials, one prospective and one retrospective, of chorioretinitis treated with atovaquone, there appeared to be a lower recurrence rate of eye lesions than in historical benchmarks using pyrimethamine and sulfadiazine [28,29]. Adding on clindamycin to atovaqu one synergistically enhanced clearance of brain cysts in animals [23] and clindamycin has already been used for congenital toxoplasmosis in children with sulfadiazine allergy or G6PD deficiency [7].

Itraconazole may be a good second choice if it can be shown to reduce brain cysts in additional animal studies. The drug has been studied in neonates for tinea capitis and may not need serum concentration monitoring as in life-threatening infections [30-32]. Spiramycin is already used in some centers for the treatment of congenital toxoplasmosis and metronidazole is commonly used for neonatal anaerobic infections. Metronidazole lacks anti-Toxoplasma activity and instead functions to increase brain concentrations of spiramycin by inhibition of multidrug-resistant protein 2 and P-glycoprotein [15] Metronidazole, however, lowers the seizure threshold, and neonates with congenital toxoplasmosis are predisposed to seizures, likely limiting the use of this drug in severe congenital toxoplasmosis. Similarly, didanosine is FDA approved for treatment of HIV infection in neonates over 2 weeks of age; however, it is currently not recommended as a first-line agent due to significant toxicities [27].

Collectively, atovaqu one and the other listed drugs represent a potential path forward in the treatment of congenital toxoplasmosis. The agents used against toxoplasmosis have remained largely unchanged since the 1950s, despite continued poor outcomes for many patients [33]. Researchers and funders should prioritize evaluation of adjunctive agents against the Toxoplasma bradyzoite with the hope of reducing long-term complications of congenital toxoplasmosis.

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