Congenital Toxoplasmosis: Time for a New Treatment Approach

Sam D Chorlton*

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

Submission: July 19, 2017; Published: July 25, 2017

*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 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 reanimate.
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.

Atovaquone 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 atovaquone 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, atovaquone 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.

References

1. Varella IS, Canti IC, Santos BR, Coppini AZ, Argondizzo LC, et al. (2009) Prevalence of acute toxoplasmosis infection among 4,111 pregnant women and the mother-to-child transmission rate in a public hospital in South Brazil. Mem Inst Oswaldo Cruz 104(2): 383-388.
2. Guerina NG, Hsu HW, Meissner HC, Maguire JH, Lynfield R, et al. (1994) Neonatal semologic screening and early treatment for congenital Toxoplasma gondii infection. N Engl J Med 333(26): 1858-1863.
3. Wallon M, Garweg JG, Abrahamowitz M, Cornu C, Vinault S, et al. (2014) Ophthalmic outcomes of congenital toxoplasmosis followed until adolescence. Pediatrics 133(3): 601.
4. Cook AJ, Gilbert RE, Bufolano W, Zuferey J, Petersen E, et al. (2000) Sources of Toxoplasma infection in pregnant women: European multicentre case-control study. European Research Network on Congenital Toxoplasmosis. BMJ 321(7254): 142-147.
5. SYRCOT (Systematic Review on Congenital Toxoplasmosis) study group, Théibaut R, Leproust S, Chêne G, Gilbert R (2007) Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients’ data. Lancet 369(9556): 115-122.
6. Dubey JP, Lindsay DS, Speer CA (1998) Structures of Toxoplasma gondii tachyzoites, bradyzoites, and sporozoites and biology and development of tissue cysts. Clin Microbiol Rev 11(2): 267-299.
7. Guerina N (2017) Congenital toxoplasmosis: treatment, outcome, and prevention. UpToDate.
8. Kravetz J (2013) Congenital toxoplasmosis. BMJ Clin Evid.
9. McLeod R, Boyer K, Harrison T, Kasza K, Swisher C, et al. (2006) Outcome of treatment for congenital toxoplasmosis, 1981-2004: the National Collaborative Chicago-Based, Congenital Toxoplasmosis Study. Clin Infect Dis 42(10): 1383-1394.
10. Roizen N, Swisher CN, Stein MA, Hopkins J, Boyer KM, et al. (1995) Neurologic and developmental outcome in treated congenital toxoplasmosis. Pediatrics 95(1): 11-20.
11. Costa IN, Angeloni MB, Santana LA, Barbosa BF, Silva MC, et al. (2009) Azithromycin inhibits vertical transmission of Toxoplasma gondii in Calomys callosus (Rodentia: Cricetidae). Placenta 30(10): 884-890.
12. Sullivan WJ, Hakimi MA (2006) Histone mediated gene activation in Toxoplasma gondii. Mol Biochem Parasitol 148(2): 109-116.
13. Neville AJ, Zach SJ, Wang X, Larson JJ, Judge AK, et al. (2015) Clinically available medicines demonstrating anti-Toxoplasma activity. Antimicrob Agents Chemother 59(12): 7161-7169.
14. Montazeri M, Sharif M, Sarvi S, Mehrzadi S, Ahmadpour E, et al. (2017) A systematic review of in vitro and in vivo activities of anti-Toxoplasma drugs and compounds (2006-2016). Front Microbiol 8: 25.

15. Chew WK, Segarra I, Ambu S, Mak JW (2012) Significant reduction of brain cysts caused by Toxoplasma gondii after treatment with spiramycin coadministered with metronidazole in a mouse model of chronic toxoplasmosis. Antimicrob Agents Chemother 56(4): 1762-1768.

16. Sarciron ME, Lawton P, Saccharin C, Petavy AF, Peyron F (1997) Effects of 2'-3'-dideoxyinosine on Toxoplasma gondii cysts in mice. Antimicrob Agents Chemother 41(7): 1531-1536.

17. Issa MM, Barakat AM, Amer EI, Younis LK (2015) Could miltefosine be used as a therapy for toxoplasmosis? Exp Parasitol 157: 12-22.

18. Martins-Duarte ES, Lembregter L, de Souza W, Vommaro RC (2010) Toxoplasma gondii: Fluconazole and itraconazole activity against toxoplasmosis in a murine model. Exp Parasitol 124(4): 466-469.

19. Araujo FG, Huskinson-Mark J, Gutteridge WE, Remington JS (1992) In vitro and in vivo activities of the hydroxynaphthoquinone 566C80 against the cyst form of Toxoplasma gondii. Antimicrob Agents Chemother 36(2): 326-330.

20. Ferguson DJ, Huskinson-Mark J, Araujo FG, Remington JS (1994) An ultrastructural study of the effect of treatment with atovaquone in brains of mice chronically infected with the ME49 strain of Toxoplasma gondii. J Exp Pathol 75(2): 111-116.

21. Araujo FG, Lin T, Remington JS (1993) The Activity of atovaquone (566C80) in murine toxoplasmosis is markedly augmented when used in combination with pyrimethamine or sulfadiazine. J Infect Dis 167(2): 494-497.

22. Gormley PD, Pavesio CE, Minnasian D, Lightman S (1998) Effects of drug therapy on Toxoplasma cysts in an animal model of acute and chronic disease. Invest Ophthalmol Vis Sci 39(7): 1171-1175.

23. Djurkovic-Djakovic O, Milenkovic V, Nikolic A, Bobic B, Grujic J (2002) Efficacy of atovaquone combined with clindamycin against murine infection with a cystogenic (Me49) strain of Toxoplasmagondii. J Antimicrob Agents Chemother 50(6): 981-987.

24. Hughes W, Dorenbaum A, Yogev R, Beauchamp B, Xu J, et al. (1998) Phase I safety and pharmacokinetics study of micronized atovaquone in human immunodeficiency virus-infected infants and children. Pediatric AIDS Clinical Trials Group. Antimicrob Agents Chemother 42(6): 1315-1318.

25. Hudson A (1993) Atovaquone—a novel broad-spectrum anti-infective drug. Parasitol Today 9(2): 66-68.

26. U.S. Food, Drug Administration (2000) MALARAONE (atovaquone and proguanil hydrochloride) pediatric tablets.

27. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (2017) Guidelines for the use of antiretroviral agents in pediatric HIV infection.

28. Pearson PA, Piracha AR, Sen HA, Jaffe GJ (1999) Atovaquone for the treatment of toxoplasma retinochoroiditis in immunocompetent patients. Ophthalmol 106(1): 148-153.

29. Winterhalter S, Severing K, Stammen J, Maier AK, Godehardt E, et al. (2010) Does atovaquone prolong the disease-free interval of toxoplasmic retinochoroiditis? Graefes Arch Clin Exp Ophthalmol 248(8): 1187-1192.

30. Binder B, Richtig E, Weger W, Ginter-Hanselmayer G (2009) Tinea capitis in early infancy treated with itraconazole: a pilot study. J Eur Acad Dermatol Venereol 23(10): 1161-1163.

31. Gupta AK, Dlova N, Lynde CW, Hofstader S, et al. (2001) Therapeutic options for the treatment of tinea capitis caused by Trichophyton species: griseofulvin versus the new oral antifungal agents, terbinafine, itraconazole, and fluconazole. Pediatr Dermatol 18(5): 433-438.

32. Weiss LM, Dubey JP (2009) Toxoplasmosis: A history of clinical observations. Int J Parasitol 39(8): 895-901.