Adjunctive bradyzoite-directed therapy for reducing complications of congenital toxoplasmosis

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A B S T R A C T

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 and eyes which are resistant to the currently accepted therapy of pyrimethamine and sulfadiazine. These cysts commonly reactivate later in life causing chorioretinitis and visual impairment, and rarely cause neurological complications. I hypothesize that adjunctive, bradyzoite-directed therapies have the potential to alleviate a significant burden of disease by reducing cyst burden in neonatal brain and eyes. Atovaquone may prevent Toxoplasma-associated chorioretinitis recurrence. Clinical trials are needed to evaluate it and other potential drugs as adjunctive treatment in congenital toxoplasmosis.

Introduction

Congenital toxoplasmosis continues to exact a significant toll on infants around the world, despite complicated prevention and treatment. Between 0.5/1000 and 3.4/1000 live births are affected with the disease depending on geographical region, resulting in 190 100 incident cases per year and 1.20 million DALYs [1]. Clinical presentation of the disease ranges from asymptomatic to severe neurological impairment and death [2]. At birth, a majority of infected neonates are asymptomatic; affected neonates can present with chorioretinitis, hydrocephalus, seizures and intracranial calcifications [2]. Both asymptomatic and symptomatic treated infants are at risk for late ophthalmologic and neurodevelopmental complications. In a prospective study of 477 infants with congenital toxoplasmosis, treated with standard therapy and followed for a median of 10.5 years, the cumulative probability of new retinal lesions was 48% by 20 years of age [3]. The WHO has estimated that chorioretinitis occurs in 39% of North American and European cases of congenital toxoplasmosis, and 90% of South American cases, while other studies have shown rates as low as 26% [1,4]. In about 1–2% of cases, treated infants also go on to develop neurodevelopmental complications, including developmental delay, seizures and hydrocephalus [3–5].

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, water, or undercooked meat [6]. 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 [7]. 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 within the brain and eyes [8].

Postnatal treatment guidelines for congenital toxoplasmosis suggest a combination of pyrimethamine, sulfadiazine or sulfadoxine, and folic acid for one year [2]. This recommendation is based on expert opinion and observational studies showing a lower incidence of long term complications compared with shorter treatment in historical controls, although there are also significant risks of treatment including neutropenia, thrombocytopenia, megaloblastic anemia, allergic reaction and renal failure [9,10]. More importantly, however, is the lack of activity of these drugs against the bradyzoite stage of T. gondii. Periodically and for unknown reasons, bradyzoites reactivate causing overt disease and the aforementioned late complications of congenital toxoplasmosis [11,12]. In fact, pyrimethamine and sulfadiazine therapy have enhanced conversion of tachyzoites into bradyzoites in some animal models, possibly by increasing cellular stress [13–15].

The hypothesis

Given the high rate of disease recurrence caused by bradyzoite
reactivation in infants treated for congenital toxoplasmosis, bradyzoite-directed therapy, in addition to standard postnatal therapy, has the potential to reduce a significant burden of late complications.

Evaluation of the hypothesis

There is no evidence, to my knowledge, directly looking at bradyzoite-directed therapy and disease recurrence. However, several lines of evidence support the hypothesis that reducing cyst burden, even if not eliminating it, would reduce risk for disease recurrence in congenital infection. First, in humans with Toxoplasma encephalitis, a greater number of patients with recurrence of encephalitis, compared with first episode encephalitis, have bradyzoite specific markers detected in their CSF, suggesting that bradyzoite presence is specifically associated with relapse [16,17]. Secondly, a greater proportion of mice inoculated with a higher number of cysts, either via ingestion or subcutaneous injection, develop acute toxoplasmosis compared with mice inoculated with a lower number. Mice inoculated with higher burdens of cysts also have more severe disease when they do develop it [18–20]. Finally, in a model of chronically infected mice undergoing immunosuppression, mice that developed Toxoplasma encephalitis had a 6-fold increase in the number of brain cysts compared with mice that underwent the same immunosuppression but did not develop encephalitis [21]. Taken together, these findings show that cyst presence and number are likely causal factors in predicting toxoplasmosis recurrence.

Two recent reviews highlight currently approved and investigational drugs with activity against the bradyzoite stage of Toxoplasma gondii and the potential to decrease cyst burden [22,23]. Notably, animal studies have demonstrated activity of spiramycin combined with metronidazole, itraconazole, atovaquone (with or without clindamycin), guanabenz, didanosine, and miltefosine against chronic Toxoplasma infection in vivo [24–35]. All of these agents are approved for use in humans, and some of these agents are established and safe in pediatrics. In this section, I review support for what I consider to be some of the most promising therapeutic research hypotheses.

Atovaquone

Atovaquone is perhaps the most promising adjunctive agent for further evaluation given its low side effect profile, selective antiparasitic activity, single drug administration, lack of interaction with standard congenital toxoplasmosis therapy, and FDA approval for other pediatric disease (ie malaria with proguanil) [36,37].

In animal studies of chronic Toxoplasma infection, atovaquone has been shown to reproducibly and reliably reduce the number of brain cysts [28,29,31,32,34,35]. Compared with pyrimethamine and sulfadiazine, atovaquone was significantly superior in reducing the number of brain cysts in models of both acute and chronic toxoplasmosis [31]. In the acute model, where mice were treated upon the first sign of retinal lesions for a total of 4 weeks, atovaquone-treated mice had a mean of 1.5 (SEM 0.52) cysts per whole brain. This number was compared with control-treated or pyrimethamine- and sulfadiazine-treated mice, which had a mean of 12.89 (SEM 2.91) and 8.4 (SEM 1.93) cysts per brain, respectively (p < 0.05). In the chronic model, where treatment was started 12 weeks after Toxoplasma inoculation of the mice, atovaquone-treated mice had 17.4 cysts per brain, compared with 318 in the control group and an unspecified but similar (to the control) number in the pyrimethamine- and sulfadiazine-treated group. Numbers of cysts in animal eyes in this trial were too small for meaningful between-group analysis. Some evidence also suggests that the addition of clindamycin to atovaquone synergistically enhances clearance of brain cysts in mice [32]. Whether this effect is specific to clindamycin, or applies to atovaquone combined with sulfadiazine and pyrimethamine is unknown. Clindamycin has already been recommended and used for congenital toxoplasmosis in children with sulfadiazine allergy or G6PD deficiency, but as coexistence of these conditions is rare, it is infrequently used [38].

In humans, atovaquone has been successfully used for acute toxoplasmosis in adults, either in combination with pyrimethamine and folinic acid, or with sulfadiazine, or as a single agent [39–41]. In two uncontrolled trials, one prospective and one retrospective, of choriorretinitis treated with atovaquone, there appeared to be a lower recurrence rate of eye lesions than in historical benchmarks using other antiparasitics [42,43]. Winterhalter et al. show that at 2 years, 27% of their 41 patients had disease recurrence, compared with 35% and 53% in select other studies [42,44,45]. Pearson et al. found that in 16 patients completing treatment for choriorretinitis, only 1 developed disease recurrence during an average follow up of 10 months [43]. These studies, however, are severely limited by their observational nature and lack of direct comparison.

In other studies of acute toxoplasmosis in humans, atovaquone has had high rates of failure and relapse [40,41,46,47]. Through these early trials and animal studies, it was realized that atovaquone should not be used alone and was synergistic when used in combination with other anti-Toxoplasma therapies [30,48]. The ACTG 237/ANRS 039 study showed that atovaquone used in combination with pyrimethamine or sulfadiazine had comparable response and relapse rates to standard combination therapy in AIDS patients with Toxoplasma encephalitis. No trials have evaluated atovaquone in addition to two-drug standard therapy, either for acute outcomes or relapse rates.

The last disadvantage of atovaquone is its cost. In 2007, atovaquone was noted to cost €116 per week in comparison to pyrimethamine (€6.50 per week), sulfadiazine (€25 per week) and clindamycin (€30 per week) [49]. However, given the large burden of disease caused by recurrent toxoplasmosis, some have postulated that atovaquone therapy would be cost-saving [42].

Other potential agents

Spiramycin has historically been used in some centers for postnatal treatment of congenital toxoplasmosis; however, since 2001 it has been phased out given limited CNS penetration and parasitostatic action [2]. Chew et al. showed that spiramycin, coadministered with metronidazole, reduced the number of brain cysts 15-fold compared with placebo in mice after just one week of therapy [24]. In this model, metronidazole functioned by increasing brain spiramycin AUC∞ by 64%, likely by inhibition of multidrug-resistant protein 2 and P-glycoprotein. Metronidazole is commonly used for neonatal anaerobic infections, and is generally well tolerated. There are no interactions of this combination with standard therapy. One potential drawback is that metronidazole lowers the seizure threshold, and neonates with congenital toxoplasmosis are predisposed to seizures, possibly limiting the utility of this combination.

The antifungal itraconazole has also been shown to reduce brain cysts in an animal model [27]. Interestingly, itraconazole achieves negligible CSF concentrations but high brain parenchymal concentrations [50]. Haynes et al. found that brain parenchymal concentrations of hydroxyl-itraconazole, the active metabolite of itraconazole, approached those measured in serum of mice with Histoplasma meningitis [51]. In efficacy studies, itraconazole has had comparable efficacy with fluconazole in an animal model of coccidiodial meningitis and in some, but not all, human trials of consolidation therapy in cryptococcal meningitis [52–54]. Furthermore, despite significant interactions between azoles and other drugs, itraconazole does not appear to interact with standard congenital toxoplasmosis therapy. Given highly variable drug absorption, itraconazole usually requires serum drug level monitoring. Itraconazole can also cause hepatic dysfunction, hypokalemia, hyperptension, and peripheral edema, necessitating routine laboratory monitoring. As standard of care for congenital toxoplasmosis usually incorporates frequent bloodwork and followup of therapy toxicity, this is unlikely to be a barrier to administration.

While these drugs have been shown to reduce cyst burden in animal
models, none have been replicated in additional studies, and none have been compared against pyrimethamine and sulfadiazine. Further research is needed to confirm their efficacy in animal models before consideration of trials in humans.

Unlikely candidates

Mifepristone, guanabenz and didanosine are also drugs approved for use in humans and have been shown to reduce cyst burden, but are unlikely to be tested in congenital toxoplasmosis any time soon [25,26]. Mifepristone is a repurposed cancer drug, currently used for leishmaniasis, and exhibits embroytotoxicity and teratogenicity. Safety in children under 12 years of age has not been established, and rat studies show juveniles to be more sensitive to adverse effects including retinal degeneration and renal toxicity [55]. Similarly, there is no clinical experience for guanabenz, a retinedhypertensive, in pediatrics. Finally, didanosine has been used in pediatric HIV and exhibits significant toxicities, including a potentially fatal hepatotoxicity, and has therefore been removed from HIV guidelines [56].

Consequences of the hypothesis and discussion

At the time of writing (July 2019), there are five and two trials registered in ClinicalTrials.gov and the WHO’s International Clinical Trials Registry Platform, respectively, with keywords search is needed to confirm.

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[34] Pearson PA, Piracha AR, Sen HA, Jaife GJ. Atovaquone for the treatment of toxoplasma retinochoroiditis in immunocompetent patients11The authors have no financial interest in atovaquone or Burroughs Wellcome Co. Ophthalmology s00417-010-1379-9.

[35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] [50] [51] [52] [53] [54] [55] [56] [57]