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Case Report Open Access

Atovaquone: A Valuable Therapeutic Option in *Toxoplasma* Retinochoroiditis

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Abstract

Background: *Toxoplasma gondii* is a leading cause of severe foodborne illness in first world countries and the most common cause of posterior uveitis. Neither a standard treatment protocol has been established so far, nor has the efficacy of the mostly applied medications and their combinations be proven in well-designed clinical trials. Atovaquone, a hydroxy-1,4-naphtoquinone, is a safe and effective treatment against tachyzoites and cyst forms of *Toxoplasma*, but it is only FDA and EMEA approved for the treatment of pneumocystis infections. We have started using Atovaquone in ocular toxoplasmosis on a regular, off-label basis in 1996.

Methods: We report about the use of Atovaquone 750 mg twice daily in punctate outer retinal toxoplamosis as well as in *Toxoplasma* retinochoroiditis resistant to four different antibiotics.

Results: *Toxoplasma* activity stopped within three weeks of Atovaquone therapy without any side-effects.

Conclusions: In our hands the three-week Atovaquone treatment is a safe and efficient therapeutic option in ocular toxoplasmosis. Placebo-controlled randomized trials of anti-*Toxoplasma* treatment in patients presenting with *Toxoplasma* retinochoroiditis are required. These trials should include Atovaquone.

Keywords: *Toxoplasma gondii*; Toxoplasmosis; Retinochorioiditis; Atovaquone

Introduction

Toxoplasma gondii is a leading cause of severe foodborne illness in first world countries and the most common cause of posterior uveitis [1]. Soil contaminated with cat feces, raw or undercooked meat and transplacental transmission are the principal sources of infection.

Toxoplasma is obligate intracellular parasites (Apicomplexan coccidian protozoan). These protozoans have a sexual stage in intestinal cells of cats. Here they form oocysts passed in feces. Humans and other animals are infected by ingestion of oocyst in contaminated water, vegetables and fruits. This is the predominant source of infection in North America. Data of a recent investigation revealed that 78% of pregnant women acquired primary infection from oocyst forms [2].

In all other infected mammals tachyzoites (the intracellular living form of *Toxoplasma*) develop from ooycysts, infect nucleated host cells and utilize monocytes, macrophages, and dendritic cells as Trojan Horse to escape the host immune defense [3], to bypass the blood-brain barrier [4,5], and the placenta to spread and form a systemic disease [5]. In tissues, tachyzoites form cysts, which contain bradyzoites. Bradyzoites reproduce very slowly and asexually in these cysts, which might survive for a whole lifespan.

The ingestion of these bradyzoit-containing cysts in raw or undercooked meat is responsible for about 20% of *Toxoplasma* infections.

Congenital toxoplasmosis

It is estimated that from 4 million births each year in the United States, 400 have aquired congenital toxoplasmosis (about one case of congenital toxoplasmosis in every 10000 births) [6]. In developing countries, this number is significantly higher [7]. Congenital toxoplasmosis is instigated by the transplacental transmission of organisms in maternal infection [8]. A low number of *Toxoplasma* organisms can induce an extensive inflammatory reaction.

Toxoplasma retinochoroiditis

Toxoplasmosis is the most common cause of posterior uveitis. Ocular symptoms vary from reduced vision, strabism and nystagmus in young children to visual loss, floaters, photophobia and hyperemia in adults. Active lesions present as grey-white retinochoroidal infiltrates with adjacent vitreitis, mostly at the border of a typically pigmented chorioretinal scar. Atypical presentations include punctate outer retinitis, neuroretinitis, papillitis, pseudo-multiple retinochoroiditis, unilateral pigmentary retinopathy, Fuchs`like anterior uveitis, scleritis and multifocal of diffuse necrotising retinitis [9].

The laboratory diagnosis is based on either detection of anti-*Toxoplasma* antibodies or on detecting *Toxoplasma*-DNA using polymerase chain reaction. It is important to mention that serology is

not reliable in ocular toxoplasmosis-IgM and even IgG might be negative despite an acute intraocular *Toxoplama* retinochoroiditis.

Toxoplasmic retinochoroiditis resolves without treatment within 6-8 weeks, leaving a pigmented scar [10].

Toxoplasma therapy

Although *Toxoplasma* retinochoroiditis is the major cause of posterior uveitis, a standard treatment protocol has not been established so far, nor has the efficacy of the mostly applied medications and their combinations been proven in well-designed clinical trials.

All available drugs act primarily against tachyzoites and do not eradicate encysted forms. The most commonly used drugs target the folate pathway of the parasite. Many of the current treatment regimens are based on case series and case studies. There is no large scale trials on the efficacy of drugs used to treat toxoplasmosis [11]. Considering the safety of these treatment regimens, 40% adverse drug reactions have been reported in a retrospective chart review [12] (Table 1).

Pyrimethamin
Sulfadiazine
Clindamycin
Trimethoprime-sulfamethoxazol
Spiramycin
Azithromycin
Tetracycline
Minocycline
Dapsone
Rifabutin
Atovaquone
Intravitreal Clindamycin
Combinations
Pyrimethamine plus Sulfadiazine plus folic acid
Pyrimethamin plus Clindamycin
Pyrimethamin plus Trisulfapyrimidine
Trimethoprime plus Sulfamethoxazol plus Clindamycin

Table 1: Drugs and drug-combinations currently used to treat toxoplasmosis.

Atovaquone (Wellvone®, Mepron®)

Atovaquone, a hydroxy-1,4-naphtoquinone, is a fairly safe and effective treatment against tachyzoites and cyst forms of *Toxoplasma* [13]. Atovaquone acts by targeting mitochondrial respiration and binds to the ubiquinol oxidation on cytochrome bc1 complex to block and to collapse the membrane in the organisms [14]. Atovaquone has a half-life of 1.5-3 days and mainly binds to plasma proteins (99%) and is excreted into feces (94%) without being metabolized [15]. Atovaquone was superior to the commonly used combination of pyrimethamin plus sulfadiazine or pyrimethamine plus clindamycin therapies against brain inflammatory responses and the severity of infection in mice [16].

We report about the use of Atovaquone in *Toxoplasma* retinochoroiditis.

Material and Methods

Case 1

A 23 year old man has been referred to our clinic due to a painless visual loss in the left eye within a few days. No history of ocular trauma, surgery or prior visual impairment has been reported. The corrected visual acuity was 1.0 in the right, and 0.3 in the left eye.

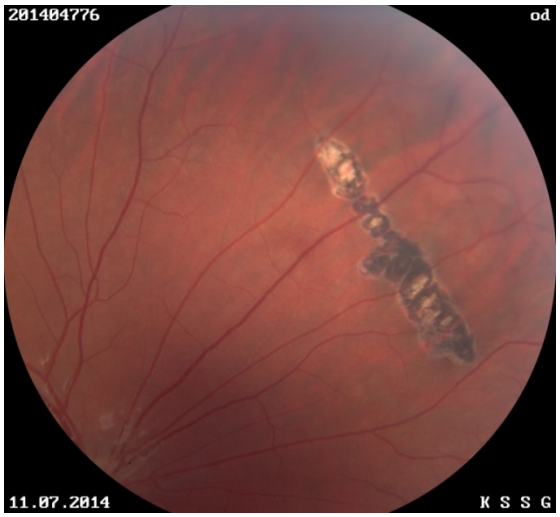

Figure 1a: Case 1: pigmented scar.

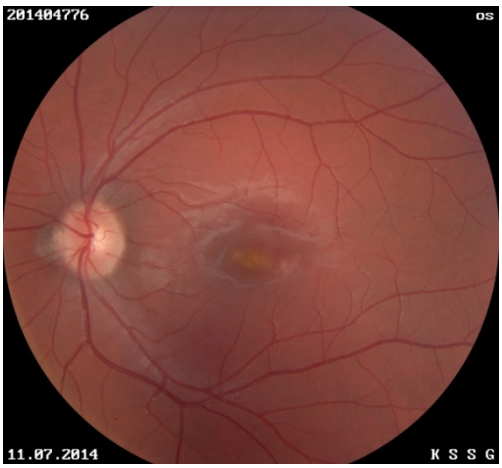

Figure 1b: Case 1: foveolar region with yellow lipofuscin-like pathology.

The anterior segments of the eye were free from inflammation. Funduscopy revealed a peripheral, pigmented scar without any signs

of inflammation in the right eye (Figure 1a pigmented scar). Both the foveolar region of the right and the left eye showed a yellow lipofuscin-like pathology (Figure 1b foveolar region with yellow lipofuscin-like pathology). Optical coherence tomography and fluorescence-angiography showed late leakage which led to the diagnosis of a punctate outer retinal toxoplasmosis (Figure 1c fluorescence-angiography-punctate outer retinal toxoplasmosis). No anti-*Toxoplasma* IgG or IgM has been found in serology. After taking the patients informed consent with the notice that this therapy is off-label, a systemic therapy with Atovaquone (Wellvone®) 750 mg twice daily for 21 days and Prednisolon (Spiricort®) 30 mg/day, reduced by 10 mg every 4 days has been started.

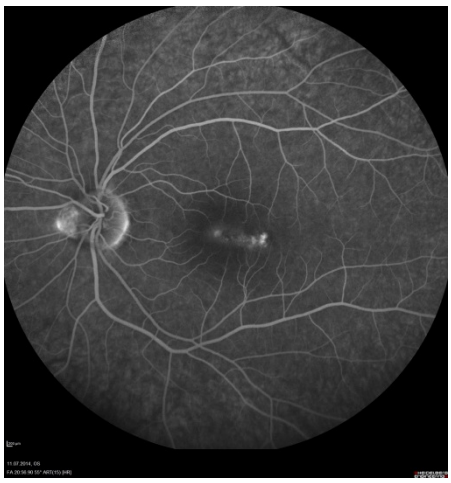

Figure 1c: Case 1: Fluorescence-angiography-punctate outer retinal toxoplasmosis.

Case 2

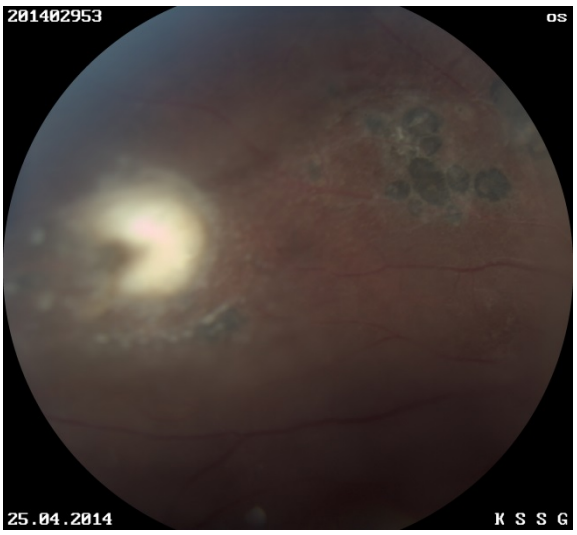

Figure 1d: Case 2: *Toxoplasma* reactivation.

A 24 year old women has been seen in our clinic for a second opinion consultation. She has been treated since seven weeks with sulfamethoxazol 800 mg plus trimethoprim 160 mg twice daily (Bactrim forte®) plus clindamycin 300 mg 4x/day (Dalacin®) and prednisolon 30 mg due to a *Toxoplasma* reactivation with severe inflammation and infiltration of the vitreous body in the left eye (Figure 1d *Toxoplasma* reactivation).

This was the first reactivation in the left eye, the right eye was amblyopic due to anisometropia. She complained no improvement in visual acuity and floaters in her only functional eye despite systemic therapy. Best corrected visual acuity was 0.1 in the amblyopic right and 0.5 in the left eye. The anterior segments showed no inflammatory activity. Funduscopy revealed dense retinochorioidal inflammation adjacent to a chorioretinal scar with a corresponding vitreal infiltration in her left eye.

We suggested changing therapy to atovaquone. As atovaquone (Wellvone®) is only licensed to treat pneumocystis carinii, the referring eye clinic preferred to change therapy to doxycyclin 200 mg twice daily plus prednisolon 30 mg. This second therapeutic regimen has been applied for another eight weeks. After a total of 15 weeks of systemic antibiotic and steroid-therapy the patient showed up again in our clinic. Visual acuity in the left eye was still 0.5 and inflammatory activity did not change under clindamycin plus steroids.

After taking the patients informed consent we started atovaquone (Wellvone®) 750 mg twice daily for 21 days.

Results

Case 1: Punctate outer retinal toxoplasmosis. Atovaquone 750 mg twice daily has been applied for three weeks. In the ophthalmic examination four weeks after the initiation of this systemic therapy visual acuity in the left eye rose from 0.3 to 1.0. No side effects have been reported.

Case 2: Resitance against four different antibiotics.

As the young patient already showed signs of a Cushing`s syndrome due to the prolonged systemic steroidtherapy we decided to stop this therapy and started Atovaquone 750 mg twice daily for three weeks. Despite the discontinuation of systemic steroids, the patient's condition improved. In the opthalmic examination after four weeks the visual acuity had improved to 1.0 in the left eye. The retinochorioidal lesion transformed to a pigmented scar. The vitreal infiltration turned to postinflammatory degenerative floaters. No side effects have been reported.

Discussion

We report about an unusual case of a punctate outer retinal toxoplasmosis which has been treated succesfully without any side effects. It is an important example, that despite the intraocular *Toxoplasma* activity, serology might be negative.

In a second case, we report about the use of Atovaquone in *Toxoplasma* uveitis, which has been resistant to antibiotic therapy. In this case, intraocular *Toxoplasma* showed an unusually long activity for more than 15 weeks despite systemic anti-*Toxoplasma* therapy. With Atovaquone, the inflammatory activity stopped within three weeks, despite the discontinuation of systemic steroids. This close time-effect relationship suggests a superior anti-*Toxoplasma* effect of Atovaquone as shown experimentally [16].

Toxoplasma gondii is the leading cause of posterior uveitis. It is mostly caused by reactivation of a congenital *Toxoplasma* infection adjacent to a typically pigmented chorioretinal scar. In most cases the chorioretinal inflammation and its epifocal vitreitis resolve without treatment within 6-8 weeks. If the retinochoroidal inflammation is in close proximity to the macula or the accompanied vitreal infiltration is severe, systemic therapy against *Toxoplasma* plus systemic steroids may be indicated. But until now, no antibiotic treatment protocol has been proven to be effective with regard to visual acuity or recurrence-rate [17].

This is especially disturbing when considering that *Toxoplasma* is the most important cause of posterior uveitis.

Atovaquone might expand our therapeutic armamentarium against *Toxoplasma*. Atovaquone is rarely used in the treatment of ocular Toxoplasmosis. This is due to the fact that Atovaquone is only FDA and EMEA certified for Pneumocystis carinii infections. If used for treating Toxoplasmosis it is "off-label". Therefore it is the responsibility of the treating doctor to take the patients informed consent, when starting this treatment protocol. We have started using Atovaquone in ocular toxoplasmosis in 1996 [18]. In our hands the three-week treatment is well tolerated. We routinely ask the patient about side effects. No side effects have been reported so far.

As reported by Stanford et al. there is a lack of evidence to support routine antibiotic treatment for acute toxoplasmic retinochoroiditis [17]. Placebo-controlled randomized trials of anti-*Toxoplasma* treatment in patients presenting with toxoplasmic retinochoroiditis are required. These trials should include Atovaquone.

Conflict of Interest Statement

None of the authors has a proprietary interest in any material or method described.

Patients Consent to Publication

The patients gave their consent for all or any part of this material to appear in this journal, and any other works or products, in any form or medium.

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