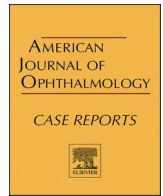




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# Use of a slow-release intravitreal clindamycin implant for the management of ocular toxoplasmosis

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## ABSTRACT

**Purpose:** To report the first patient with ocular toxoplasmosis treated with a slow-release biodegradable intravitreal clindamycin implant.

**Observations:** A 39-year-old human immunodeficiency virus (HIV)-positive woman with recurrent toxoplasmic retinochoroiditis and vitritis for whom oral medication was medically contraindicated was treated with an intravitreal slow-release clindamycin implant and three monthly intravitreal injections of clindamycin and dexamethasone. Serial ophthalmologic examinations demonstrated gradual, complete resolution of posterior uveitis and healing of the retinochoroidal lesion with cicatricial changes, as well as gradual improvement of cells in the anterior chamber. There was no significant change in electroretinography waves after treatment with the implant. The presence of the implant, or part of it, was detectable in the vitreous cavity for 4 months. To date, the patient has been monitored for 30 months, and there has been no reactivation of ocular toxoplasmosis.

**Conclusion:** The slow-release clindamycin implant was safe for intravitreal use in this patient and may have contributed to the long-term control of toxoplasmosis chorioretinitis.

## 1. Introduction

Toxoplasmosis is caused by the protozoan *Toxoplasma gondii*, and is the most common cause of infectious posterior uveitis.<sup>1</sup> It can be transmitted by ingestion of the protozoan through contaminated foods and fluids, or by the transplacental route, organ transplantation, or blood transfusion.<sup>2</sup> About one-third of the world's population may be infected with toxoplasmosis.<sup>2</sup> *T. gondii* seropositivity can range from 10% to 90% and may be asymptomatic or may manifest with various clinical signs and symptoms depending on the immunological status of the patient.<sup>1,3</sup>

The prevalence of posterior uveitis caused by toxoplasmosis is about 17.7% in southern Brazil, and in the United States 2% of *T. gondii*-infected patients have ocular signs of the disease.<sup>4,5</sup> Ocular toxoplasmosis usually occurs as focal exudative retinochoroiditis, although it can

also manifest in an atypical manner as punctate outer retinitis, Jensen neuroretinitis, or even as a necrotizing condition.<sup>1</sup>

In most cases, the treatment of ocular toxoplasmosis consists of orally administered drugs. The traditional regimen is a combination of sulfadiazine, pyrimethamine, and folinic acid, with or without the use of oral steroids, although sometimes just sulfamethoxazole/trimethoprim is administered. Clindamycin and azithromycin are alternatives for patients who are allergic to other treatment regimens.<sup>6</sup> However, oral treatments may induce undesirable side effects. Helfenstein M et al. reported a 24.3% rate of adverse reactions to the classic regimen (sulfadiazine, pyrimethamine and folinic acid) which led to discontinuation of the medication; reported adverse events included elevated creatinine (5.4%), increased hepatic enzyme levels (5.4%), vomiting (5.4%), skin rashes (5.4%, and facial edema (2.7%).<sup>7</sup> A retrospective study reported a 40% incidence of adverse effects related to the medications commonly

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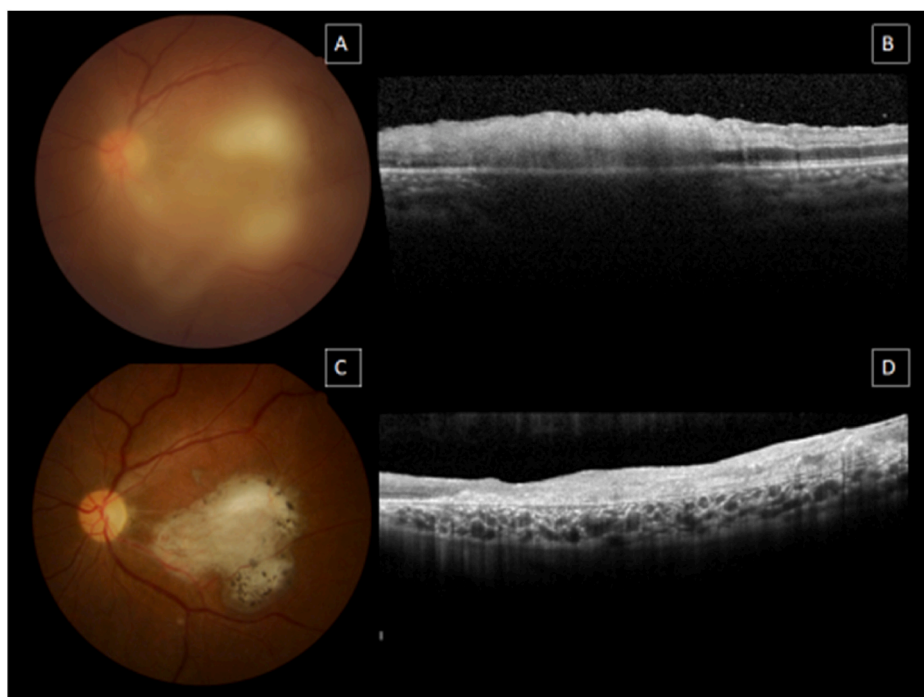
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**Fig. 1.** Multimodal evaluation of the left eye before treatment with intravitreal implant. **A-** Vitritis; exudative lesion with ill-defined margins in the macula. **B-** OCT shows thickened homogeneous hyperreflectivity within the retinal layers consistent with full-thickness retinal involvement of the active lesion. Multimodal evaluation after treatment with a clindamycin implant **C-** Healed lesion in the macula. **D-** OCT shows reduction of retinal edema and of cells, atrophy and disorganization of the retinal layers, and loss of the foveal contour.

used (sulfadiazine, pyrimethamine, sulfamethoxazole-trimethoprim, clindamycin, and atovaquone), among them skin rashes, diarrhea, gastrointestinal bleeding, epigastric pain, leukopenia, and thrombocytopenia.<sup>8</sup> Thus, other therapeutic options have been proposed. Kishore K et al. reported resolution of the inflammatory process with improved visual acuity among patients with ocular toxoplasmosis treated with intravitreal injections of 1.0 mg clindamycin in 0.1 mL and 1.0 mg of dexamethasone in 0.1 mL.<sup>9</sup> However, multiple injections of these agents may be required to control the disease, thereby increasing the risk of complications.

Clindamycin is a medication belonging to the lincosamide group and is considered to be a bacteriostatic agent that penetrates the intracellular medium and inhibits the synthesis of bacterial proteins. It affects apicoblast translation, rendering the microorganisms more vulnerable to opsonization and phagocytosis, which facilitates their digestion by leukocytes.<sup>10</sup>

We report herein a case of an immunosuppressed and sulfa drug-intolerant patient with posterior uveitis due to toxoplasmosis, who was medically unable to be treated with the medication regimen traditionally used to treat ocular toxoplasmosis and, therefore, was treated with a slow-release intravitreal clindamycin implant, the safety of which was demonstrated by Fernandes-Cunha et al.<sup>13</sup>

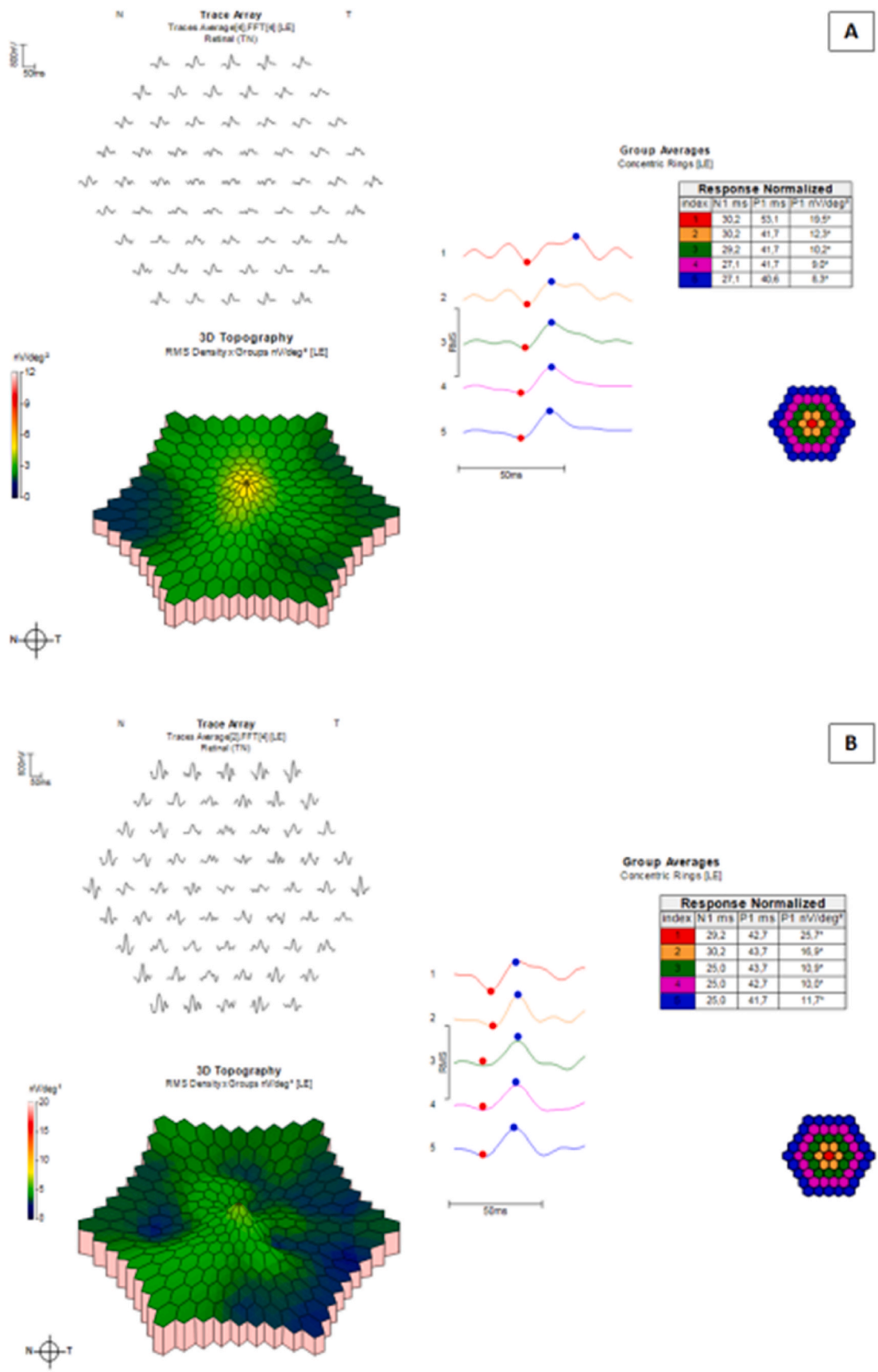
### 1.1. Case report

A 39-year-old woman presented with a one-week history of reduced visual acuity, conjunctival injection, photophobia and pain in the left eye which had not improved after four days of treatment with dexamethasone and tropicamide eyedrops and oral sulfamethoxazole/trimethoprim prescribed by her primary eye doctor. Her visual acuity was 20/20 in the right eye (OD) and 20/200 in the left eye (OS). Slit-lamp biomicroscopy of the right eye was unremarkable and, in the left eye, revealed mild conjunctival injection, anterior chamber cells (ACC) 2+/4+, and fine diffuse keratic precipitates (KP). Dilated funduscopic examination was unremarkable in the right eye and, in the left eye, revealed mild vitritis and a yellow-white retinochoroidal lesion with overlying exudation occupying the entire posterior pole. Serological IgM and IgG tests were positive for toxoplasmosis. Therefore, oral

sulfamethoxazole 800mg/trimethoprim 160mg every 12 hours, oral prednisone 40 mg once daily and topical dexamethasone and tropicamide were continued. In addition to toxoplasmosis, serological investigation demonstrated human immunodeficiency virus (HIV)-positivity, with a CD4 count of 143 cells/mm<sup>3</sup> and a viral load of 126,305 copies/ml. Other common causes of retinochoroiditis in Brazil, such as syphilis and tuberculosis, were excluded with laboratory testing. Anti-retroviral treatment was initiated 30 days after initiation of ocular toxoplasmosis treatment and monitored by infectious disease specialists, and serial ophthalmologic examinations over the subsequent 45 days demonstrated gradual improvement in visual acuity (20/100 in OS), anterior (absence of anterior chamber reaction) and posterior segment inflammation (absence of vitritis), and retinochoroiditis (hypochromic lesion without exudation). After 45 days of treatment, prophylactic sulfamethoxazole/trimethoprim, three days per week, was prescribed.<sup>14</sup>

One month after prophylactic medication use, the patient presented with pharmacodermia (face, neck, chest and abdomen skin eruptions and erythema) and her clinical situation worsened, with reactivation of the chorioretinal lesion in the left eye. At this time, her visual acuity in the left eye was hand motion. Optical coherence tomography (OCT) was unremarkable in the right eye and, in the left eye, revealed disorganization of retinal architecture, increased central subfield thickness (548  $\mu$ m), and the presence of hyperreflective points on the retinal surface suggestive of inflammatory cells (Fig. 1A and B). Treatment with the typical anti-toxoplasmosis oral medications was contraindicated due to elevated liver enzymes and adverse skin effects. The patient also could not afford oral clindamycin. Intravitreal injections of clindamycin (1 mg) and dexamethasone (1 mg) were performed in the same setting. Forty-five days after this single intravitreal procedure, Best-corrected visual acuity (BCVA) improved to 20/1600 and there was partial improvement of eye fundus findings.

Given the clinical improvement noted after the administration of intravitreal therapy, and considering the medical contraindication to oral medications in this patient, treatment with an intravitreal implant of slow-release clindamycin was proposed. The implant consisted of poly lactic-co-glycolic acid (PLGA)/poly(lactic acid) (PLA), contained 0.3 mg clindamycin, and measured 0.45 mm in diameter and 6 mm in length. After obtaining written informed consent from the patient, the slow-



**Fig. 2.** Multifocal electroretinogram in left eye. **A-** Before treatment with intravitreal implant, there is a decreased foveal response, secondary to macular inflammatory changes. **B-** After treatment, there is still a reduced foveal wave amplitude response, but with higher amplitudes compared to baseline in the perifoveal area.

release clindamycin implant was injected into the vitreous cavity using a 25-gauge trocar-cannula as describe by Cunha et al.<sup>11</sup> Topical dexamethasone with vigamox (Vigadexa®) 4 times a day was prescribed for 7 days after the procedure. One day after the injection of the implant, intraocular inflammation was similar to preoperative parameters, and examination of the left eye demonstrated a BCVA of 20/1600, 3+ ACC, 2+ vitritis, intraocular pressure (IOP) of 10 mmHg, and no signs of ocular toxicity or endophthalmitis. Fifteen days after injection of the implant, examination of the left eye demonstrated stable BCVA, 1 + ACC, 1+ vitritis, and the chorioretinal lesion was in the healing process.

After a single injection of the slow-release clindamycin implant, three monthly intravitreal injections of 0.1 mL clindamycin + dexamethasone were administered (at months one, two and three following injection of the slow-release clindamycin implant), and there was progressive improvement of ocular signs and symptoms, with healing of the macular lesion and no episodes of recurrence. At last follow-up, 30 months after injection of the implant, the patient has a BCVA of 20/1600, no ACC or vitritis, and the lesion has no exudation, only atrophy and retinal disorganization. There has been a reduction of retinal edema and thickness (current OCT-measured central retinal thickness is 210 µm) with healing of the retinochoroidal lesion and no signs of active inflammatory infiltration (Fig. 1C and D). There was no clinical evidence of toxicity to the cornea, lens, retina or optic nerve.

Before insertion of the implant, multifocal electroretinogram (ERG) showed a reduced central response in the left eye, consistent with active inflammation. After resolution, multifocal ERG showed similar or higher wave amplitudes compared to the baseline examination, reinforcing clindamycin intravitreal implant safety (Fig. 2).

## 2. Discussion

The patient described herein had posterior uveitis and chorioretinitis due to toxoplasmosis and, given her HIV-positive status and associated anti-retroviral treatment, a high risk of ocular toxoplasmosis recurrence without the ability to take sulfamethoxazole/trimethoprim for prophylaxis against such recurrence.<sup>12</sup> In addition, given her immunosuppressed status, the patient was at increased risk of endophthalmitis, which made her a less favorable candidate for multiple intravitreal injections of clindamycin. The patient had no financial means for the acquisition of clindamycin for oral use. For this reason, we opted for the compassionate use of a slow-release clindamycin intravitreal implant that would release the drug and protect the retina of the patient for a much longer time than a simple intravitreal injection of the drug.<sup>10</sup> According to studies conducted in rabbits, the implant can release doses of clindamycin four times higher than a simple intravitreal injection and above the 50% inhibitory concentration for *Toxoplasma gondii* for at least six weeks.<sup>16</sup>

The ≥6-week period of clindamycin release is of high interest, especially for treating immunosuppressed patients and also patients with a high rate of disease recurrence. In our patient, the implant was visible in the vitreous cavity for four months and the patient has been free of disease recurrence for 30 months.

The clinical improvement observed in this patient, with gradual resolution of intraocular inflammation and healing of the retinochoroidal lesion with cicatricial changes, suggests that the implant, in addition to the three intravitreal injections she had received previously, may have contributed to the control of the parasite. Kishore K et al. reported improvement of toxoplasmosis chorioretinitis after intravitreal injections of 1.0 mg clindamycin and 1.0 mg of dexamethasone. In our patient, there was no reduction of inflammation immediately after the insertion of the clindamycin implant and, for this reason, three monthly intravitreal injections of the aqueous form of clindamycin in combination with dexamethasone were administered. We hypothesize that drug release from the implant was not initially sufficient to control the parasite infection. The fact that we did not inject dexamethasone in combination with the implant may have delayed the regression of the

inflammatory component of the disease process. Another hypothesis is that clindamycin takes some time to act on parasite replication.<sup>10</sup> Finally, it important to point out that, in addition to the intravitreal implant and injections, improvement in the patient's immune system with antiretroviral treatment may also have contributed to retinochoroiditis control.

The functional findings such as maintenance of visual acuity and ERG waves suggest that the implant is safe for intravitreal use. Fernandes-Cunha et al. have tested the safety of this implant *in vitro*, *in vivo* and *ex vivo*. The *in vitro* test involved the investigation of the toxicity of the implant in a culture of the human retinal pigment epithelial cell line ARPE-19 and of Muller cells (MIO-M1) by incubating the implant with the cells for 72 hours; no morphological deterioration of the cells was detected.<sup>13</sup> The *in vivo* test consisted of injecting a clindamycin implant into the vitreous cavity of rats. Evaluation of the anatomy using spectral domain OCT (Spectralis, Heidelberg, Germany) did not reveal any morphological changes in the retinal structure. The *ex vivo* test consisted of histological analysis of the enucleated eyes of these rats; there was no increase in the expression of markers of apoptosis, nor a reduction in the number of cells of the outer, inner or nuclear layers or of ganglion cells 30 days after the injection of the implant into the vitreous cavity.<sup>13,15,16</sup>

To our knowledge, this is the first report of the use of an intravitreal slow-release clindamycin implant for the treatment of ocular toxoplasmosis in humans. Combination treatment with the implant and intravitreal injections of clindamycin and dexamethasone was associated with regression of the retinochoroiditis and intraocular inflammation, and no safety signals were identified clinically or with ERG and OCT. Future studies including larger sample sizes and control groups are necessary to confirm the benefit of this new treatment strategy for patients with ocular toxoplasmosis.

## Authors' contributions

RJ and JMF were the authors primarily responsible for the research design. RJ, JMF,GC, IC, AC, and SLF were responsible for research execution and data acquisition. All authors were primary contributors to data analysis and interpretation. The manuscript was prepared by RJ, JMF, IUS and IC with final revisions and approval provided by all authors.

## Patient consent

Consent has been obtained from the patient.

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## Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

## Declaration of competing interest

The authors declare that there are no conflicts of interest related to this manuscript.

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