Local treatment of toxoplasmic retinochoroiditis with intravitreal clindamycin and dexamethasone

Tratamento local para a retinocoroidite toxoplásmica com clindamicina e dexametasona intravítrea

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ABSTRACT

Purpose: To report the clinical outcomes of local treatment of toxoplasmic retinochoroiditis (TRC) with intravitreal injections of clindamycin and dexamethasone.

Methods: Study population: 16 eyes (16 patients) with active TRC sparing the macula and juxtapapillary area treated with intravitreal injections of clindamycin (1 mg) and dexamethasone (1 mg) without concomitant systemic antitoxoplasmic or anti-inflammatory therapy. Measured parameters: Best-corrected visual acuity (BCVA) was measured by an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. BCVA and clinical characteristics of retinochoroiditis were assessed at baseline and at 1, 3, 6, and 12 months. Primary outcome measures: Resolution of retinochoroiditis and changes in BCVA.

Results: Control of TRC was achieved in all cases with a mean interval of 2.48 ± 1.03 weeks (2-6 weeks). A single injection of intravitreal clindamycin and dexamethasone was performed in 12 patients, and four patients required two intravitreal injections, during the follow-up period. Fourteen eyes (87.5%) improved ≥ 2 ETDRS lines of BCVA, of two or more Early Treatment Diabetic Retinopathy Study lines, BCVA remained stable in two eyes (12.5%), and no patient had decreased BCVA at the end of the follow-up period. No ocular or systemic adverse events were observed.

Conclusion: Local treatment with intravitreal injections of clindamycin and dexamethasone without concomitant systemic therapy was associated with resolution of TRC in patients without macular or juxtapapillary involvement. Intravitreal clindamycin and dexamethasone may represent a viable treatment option in patients with allergies or inadequate responses to oral medications.

Keywords: Chorioretinitis/drug therapy; Toxoplasmosis, ocular; Intravitreal injections; Clindamycin/administration and dosage; Dexamethasone/administration and dosage

RESUMO

Objetivo: *Reportar os resultados clínicos do tratamento local da retinocoroidite toxoplásmica com injeções intravítreas de clindamicina e dexametasona.*

Métodos: *População do estudo: 16 olhos (16 pacientes) com retinocoroidite toxoplásmica ativa sem comprometimento da mácula e da área juxtapapilar, tratados com injeções intravítreas de clindamicina (1 mg) e dexametasona (1 mg) sem terapia sistêmica anti-toxoplásmica ou anti-inflamatória concomitante. Procedimento de observação: A melhor acuidade visual corrigida (BCVA) foi medida através da tabela ETDRS. A BCVA e as características clínicas da retinocoroidite foram avaliadas na qualificação, primeiro, terceiro, sexto e 12º mês. Medidas do resultado principal: resolução da retinocoroidite e mudanças na BCVA.*

Resultados: *O controle da retinocoroidite toxoplásmica foi atingido em todos os casos com um intervalo médio de 2,48 ± 1,03 semanas (intervalo de 2 a 6 semanas). Uma única injeção intravítrea de clindamicina e dexametasona foi aplicada em 12 pacientes, e quatro pacientes precisaram de duas injeções durante o seguimento. Quatorze olhos (87,5%) melhoraram ≥ 2 linhas ETDRS de BCVA, a BCVA ficou estável em 2 olhos (12,5%) e nenhum paciente apresentou diminuição da acuidade visual no final do seguimento. Não foram observados eventos adversos sistêmicos ou oculares.*

Conclusão: *O tratamento local com injeções intravítreas de clindamicina e dexametasona sem terapia sistêmica concomitante esteve associado com a resolução da retinocoroidite toxoplásmica em pacientes sem comprometimento macular ou juxtapapilar. A clindamicina e dexametasona intravítrea representam um tratamento promissor em pacientes com intolerância, contraindicação ou resposta inadequada a medicação oral.*

Descritores: *Coriorretinite/quimioterapia; Toxoplasmose ocular; Injeções intravítreas; Clindamicina/administração & dosagem; Dexametasona /administração & dosagem*

INTRODUCTION

Toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii* that affects large proportions of the adult population in many countries worldwide with variable prevalence[1,2]. Ocular toxoplasmosis is the most common identifiable cause of posterior uveitis in immunocompetent patients. In some countries, up to 50% of all cases of posterior uveitis are attributable to toxoplasmosis[1-3].

Humans can be infected with *T. gondii* through ingestion or handling of undercooked or raw meat (mainly pork or lamb) contaminated with cysts, ingestion of food contaminated with oocysts excreted in the feces of infected cats, or by drinking contaminated water. Toxoplasmosis may also be acquired congenitally through transplacental transmission of *T. gondii* to the fetus during pregnancy. Ocular disease may occur months to years after the initial infection[2,4].

The retina is the primary site of ocular *T. gondii* infection; however, the choroid, vitreous, and anterior chamber may also be involved. Active lesions are characteristically a grey-white focus of retinal necrosis with secondary choroidal involvement and vitreous inflammatory haze. Scarred lesions may present with variable pigmentary changes with recurrent lesions tending to occur at the borders of retinochoroidal scars. Permanent visual impairment occurs in cases where lesions affect the posterior pole (within the macular arcade or adjacent to the optic nerve head) or due to complications of chronic inflammation (vitreous opacity, epiretinal membranes, retinal detachment)[1,2,5].

Toxoplasmic retinochoroiditis (TRC) is usually self-limiting. Untreated lesions generally begin to heal after a few weeks, although the time course is variable and active disease may persist for months in some cases. The treatment of toxoplasmosis lesions is indicated in

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cases of severe vitritis. Treatment aims to prevent retinal damage through inhibiting parasite replication during the active stage of retinitis, suppress inflammation, and reduce the risk of complications and permanent visual impairment[1,5-8].

Current treatment regimens for active TRC include combinations of sulfadiazine, pyrimethamine, clindamycin, combined trimethoprim/sulfamethoxazole, azithromycin, and atovaquone. However, there is no consensus regarding optimal treatment strategies, and patient-based studies comparing the efficacy of pharmacological agents are scarce. The most frequently used treatment combination has been pyrimethamine and sulfadiazine, with or without co-administration of systemic corticosteroids. Folinic acid is usually added to regimens containing pirimethamine to prevent the development of leukopenia and thrombocytopenia associated with pirimethamine folinic acid use. Adjuvant therapy with corticosteroids is frequently administered to diminish the duration and severity of inflammatory symptoms that accompany toxoplasmosis[1,5,6,8]. In a retrospective study, the most frequently administered drugs for the management of toxoplasmosis (clindamycin, sulfadiazine, pyrimethamine, trimethoprim-sulfamethoxazole, and atovaquone) were found to be associated with a high incidence of adverse reaction (40%), including gastrointestinal side effects, skin rash, bleeding, leucopenia, and thrombocytopenia[9].

Many studies have reported the efficacy of combination therapy with intravitreal clindamycin and dexamethasone in ocular toxoplasmosis patients with contraindication, intolerance, or a lack of response to traditional systemic therapy[10,11]. Oral clindamycin has been widely used in the treatment of ocular toxoplasmosis. In animal studies, clindamycin reduces the number of tissue cysts but has not been shown to prevent recurrent disease in humans[8]. Intravitreal administration of clindamycin has been shown to be a safe and effective procedure in the treatment and prophylaxis of bacterial endophthalmitis[12,13]. Intravitreal injection of dexamethasone has also been used safely in the treatment of a range of retinal disorders, including age-related macular degeneration and diabetic retinopathy[14,15]. Recently, the efficacy and tolerability of a dexamethasone intravitreal implant have been reported[16,17].

The purpose of this study was to report the clinical outcomes of local treatment of TRC with intravitreal injections of clindamycin and dexamethasone.

METHODS

Sixteen eyes of 16 consecutive patients with active TRC in zones 2 and 3 (sparing the macula and juxtapapillar area) treated with intravitreal injections of clindamycin and dexamethasone were prospectively evaluated. All the patients were recruited from the Uveitis Service of the Federal University of São Paulo (UNIFESP), Brazil. The study was approved by the institutional review board, and all patients provided written, informed consent before participating in the study. Ocular toxoplasmosis diagnoses were based on medical history, clinical evaluation, and the presence of serum IgG or IgM antibodies against *T. gondii*[5]. Lesion locations were reported according to retinal zones as previously described in a study of necrotizing retinal infections[18].

Patients were eligible for this study if they had an active toxoplasmic retinochoroidal lesion >2 disc diameters in size within zones 2 or 3 (sparing the macular and juxtapapillary regions) with 3-4+ vitreous inflammatory haze and visual acuity (VA) ≤20/63 (0.5 logMAR). Exclusion criteria for this study included previous use of immunosuppressive medications, HIV infection, lesions located within the major temporal arcades or juxtapapillary region (zone 1), allergy to clindamycin, and lesions smaller than two disc diameters. Only patients in whom oral treatment was not possible, due to poor prior response, intolerance, or contraindications, were included in this study. Combined systemic antitoxoplasmic or corticosteroid therapy was not used after initial intravitreal injections.

Patients were evaluated weekly until complete resolution of retinochoroidal lesions and monthly thereafter. Detailed ophthalmic examination was performed at the day of the first intravitreal injection (baseline) and at 1, 3, 6, and 12 months follow-up. Six patients were lost to follow-up and not examined at the 12-month visit. Ophthalmic evaluations included best-corrected visual acuity (BCVA) measured by an Early Treatment Diabetic Retinopathy Study (ETDRS) chart, anterior and posterior segment slit-lamp evaluation, Goldmann applanation tonometry, and dilated fundus examination using a binocular indirect ophthalmoscope. Optical Coherence Tomography and fluorescein angiography were performed at examiners' discretion. Conversion of counting fingers at 2 feet and hand-motion at 2 feet VA to Snellen equivalent was made according to the method proposed by Holladay[19] and was given values of +2.0 and +3.0 logMAR, respectively.

Treatment response and ocular toxoplasmosis resolution were determined clinically as sharpening of lesional borders, with or without hyperpigmentation, and improvement of vitreous inflammation. Intravitreal injections of clindamycin and dexamethasone were repeated in cases of retinochoroiditis progression (new active lesions or border enlargement) and/or increased vitreal inflammatory.

Intravitreal injections were performed under topical anesthesia and consisted of a preservative-free 0.1 ml solution containing 1.0 mg of clindamycin and 1.0 mg of dexamethasone and were performed through the inferotemporal pars plana 4.0 mm posterior to the limbus in phakic eyes and 3.0 mm posterior to the limbus in pseudophakic eyes, using a 27-gauge needle. Prior to injections, instillation of topical 5% povidone-iodine into the inferior conjunctival fornix was performed, and eyelid speculums were sited. After injections, intraocular pressure and retinal artery perfusion were evaluated, and patients were instructed to administer topical antibiotics for 7 days.

Statistical analyses

Statistical analyses were performed using SigmaStat 3.11 (SPSS Inc., Chicago, IL). Continuous variable data are expressed as mean ± standard deviation. Six patients were not examined at the 12-month follow-up visit; therefore, this visit was not included in statistical analyses. Changes in VA over time were analyzed by repeated measures analysis of variance with statistical significance set at $P<0.05$.

RESULTS

The mean age of the 10 women and 6 men included in this study was 34.00 ± 13.57 years (16-64 years). A single injection of intravitreal clindamycin and dexamethasone was performed in 12 patients, and four patients required two intravitreal injections, during the follow-up period. Fourteen eyes had previous episodes of TRC and two patients denied any previous history of ocular toxoplasmosis. Eleven patients received intravitreal injections of clindamycin and dexamethasone as primary treatment and had a history of recurrent disease and were either intolerant of prior treatments during previous episodes or were allergic to sulfonamides. Five patients were treated with oral medications at initial presentation; two had intolerance to systemic treatment (gastrointestinal side effects), one developed an allergic skin reaction secondary to sulfonamides, and the other two did not respond to oral treatment (a 6-week course of trimethoprim-sulfamethoxazole and prednisone). All stopped oral antitoxoplasmic and anti-inflammatory medications after the first intravitreal injection. Clinical and demographic characteristics are presented in table 1.

VA significantly improved during the follow-up period from a mean BCVA of 1.17 ± 0.71 logMAR (0.20-2.00) at baseline, to a mean BCVA of 0.65 ± 0.75 logMAR (0.00-2.00) at 1 month, 0.43 ± 0.56 logMAR (0.00-2.00) at 3 months, and 0.39 ± 0.52 logMAR (0.00-2.00) at 6 months ($P<0.001$, statistically significant difference from baseline BCVA at the 1, 3, and 6 months). The mean final BCVA of the 10 patients examined at the 12-month follow-up visit was 0.31 ± 0.61 logMAR (0.00-2.00). VA values during the follow-up period are presented in figure 1. Analysis of BCVA at the final study visit demonstrated BCVA had improved by two or more ETDRS lines in 14 (87.5%) eyes and had remained stable in two eyes (12.5%; Table 2).

Table 1. Summary of clinical and demographic characteristics of the patients with toxoplasmic retinochoroiditis (TRC) treated with intravitreal injections of clindamycin and dexamethasone

Case number	Gender	Age (years)	First episode of TRC	Duration of TRC symptoms before intravitreal injection (weeks)	Oral treatment before intravitreal injection	Number of injections	Initial BCVA	Final BCVA*
1	F	58	No	4.85	Yes	1	0.20	0.00
2	F	34	No	1.85	Yes	1	0.44	0.20†
3	F	23	Yes	4.28	No	1	0.60	0.00
4	M	30	No	1.57	No	2	0.50	0.18
5	M	37	No	12.85	Yes	1	0.50	0.00
6	F	29	No	3.57	Yes	1	2.00	1.00†
7	F	18	Yes	3.57	No	1	1.20	0.18
8	M	18	No	6.42	No	1	2.00	2.00
9	F	43	No	4.28	Yes	2	1.24	0.62†
10	M	26	No	2.00	No	1	2.00	0.62†
11	F	16	No	0.85	No	1	2.00	0.20
12	M	34	No	8.57	No	2	2.00	0.00†
13	M	32	No	1.43	No	2	0.48	0.00
14	F	45	No	2.85	No	1	2.00	0.48†
15	F	64	No	2.00	No	1	0.60	0.10
16	F	37	No	2.85	No	1	1.00	0.48

BCVA= best corrected visual acuity; F= female; M= male.
*= the final evaluation was performed 12 months after the intravitreal injection in 10 patients, and 6 months after intravitreal injection in 6 patients; †= patients that had the final evaluation 6 months after the intravitreal injection.

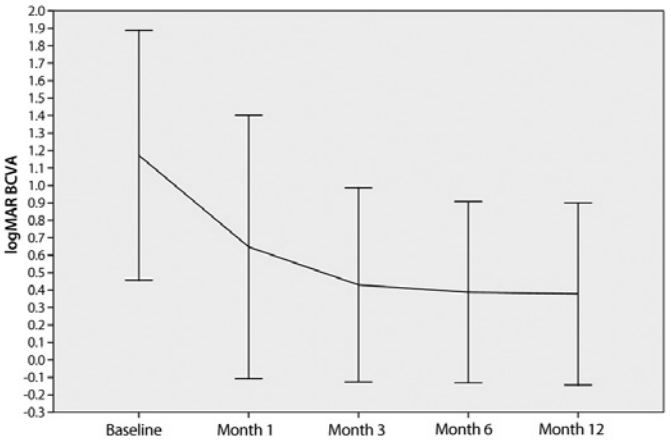

Figure 1. Graph showing changes in the mean logMAR best corrected visual acuity (BCVA) after intravitreal clindamycin and dexamethasone treatment. Error bar represents standard deviation.

Table 2. Final best-corrected visual acuity (BCVA) after intravitreal injection of clindamycin and dexamethasone compared to baseline (n=16 eyes)*

BCVA (logMAR) results	n (%)
Improved up to 2 lines	2 (12.5%)
Improved ≥3 lines	12 (75.0%)
Remained stable	2 (12.5%)

*= the final evaluation was performed 12 months after the intravitreal injection in 10 patients, and 6 months after intravitreal injection in 6 patients.

Resolution of TRC was achieved in all cases with a mean interval of 2.48 ± 1.03 weeks (2-6 weeks). Four eyes required two intravitreal injections for disease control; the mean injection interval in these patients was 29.75 ± 18.55 days (14-50 days). In one of these patients, repeated intravitreal injection was required to control disease recurrence after an initial response to the first injection performed 50 days earlier.

Episodes of worsening inflammation or decreased vision immediately after intraocular injections were not observed. During follow-up, one eye developed cataract and one eye had persistent vitreous opacities limiting VA improvement in these two eyes.

DISCUSSION

In this study, treatment with intravitreal injections of clindamycin and dexamethasone led to resolution of TRC in eyes without involvement of macular or juxtapapillary regions. Further, BCVA improved in the majority of included patients. Inflammation resolution was observed in all eyes. Evidence of ocular disease recurrence was identified in one patient during the follow-up period.

There is a lack of evidence supporting the routine use of antibiotics in the treatment of acute TRC[20]. However, treatment of ocular toxoplasmosis is usually indicated in eyes with active lesions within zone 1 of the retina, lesions larger than two disc diameters causing severe vitreitis, and immunocompromised patients with any active toxoplasmic lesion[1,5-8].

Despite the substantial range of treatment options available for toxoplasmosis, there is currently no consensus regarding optimal treatment strategies for the ocular form of toxoplasmosis. In the majority of cases, a treatment duration of at least 6 weeks requiring a frequent dosing schedule is necessary that may be associated with a high rate of adverse reactions[8,9]. These factors may limit patient adherence and negatively impact on treatment outcomes. In a study evaluating therapeutic strategies for ocular toxoplasmosis, up to 26% of patients discontinued treatment due to side effects[21].

The use of intravitreal clindamycin and dexamethasone in the treatment of ocular toxoplasmosis in patients with intolerance, contraindications, or inadequate response to oral medications has been described in case reports and case series since 1999. Martinez *et al.*[10] reported the case of a patient with reactivated ocular toxoplasmosis in the first trimester of pregnancy treated successfully with two intravitreal injections of clindamycin and dexamethasone

and systemic sulfadiazine. Eight weeks following the procedure, fundoscopic examination revealed almost complete resolution. In 2001, Kishore *et al.*[11] reported the resolution of TRC following intravitreal injections of clindamycin and dexamethasone in four eyes of four patients with concurrent systemic antitoxoplasmic medication used in three patients. All patients required two to four intravitreal injections, and responses were noted in all patients within 2 weeks of treatment. Sobrin *et al.*[22] described a case series of six patients treated with intravitreal injections of clindamycin. Five patients continued receiving systemic therapy after clindamycin injections and four underwent concomitant pars plana vitrectomy. Treatment with a single intravitreal injection of clindamycin was associated with resolution of vitreous inflammation within 6 weeks in five patients, while the sixth patient required a second injection for disease quiescence. Wong *et al.*[23] reported the case of a patient with an atypical presentation of ocular toxoplasmosis (optic disc swelling and hemispherical retinal vein occlusion) successfully treated with two injections of intravitreal clindamycin and systemic prednisolone without concomitant systemic antibiotics. In contrast, Lasave *et al.*[24] reported the use of intravitreal clindamycin and dexamethasone in 12 patients with zone 1 TRC, with eight patients receiving combined systemic antitoxoplasmic therapy, and reported resolution of retinochoroiditis with a mean number of 3.6 injections (3-6 injections) and a mean interval of 15.5 days. In a recent trial, Soheilian *et al.*[25] studied 68 patients with active toxoplasmosis randomly assigned to receive intravitreal treatment with clindamycin and dexamethasone injections or conventional oral combination therapy of pyrimethamine, sulfadiazine, and prednisolone. Comparable results in terms of reductions in lesion size, vitreous inflammation, and improvements in VA were reported between treatment groups. The mean number of injections required in the intravitreal treatment group was 1.6. In a recent prospective randomized single-blind clinical trial, Baharivand *et al.*[26] treated patients with active TRC with intravitreal clindamycin plus dexamethasone (n=32), or conventional oral therapy (n=34), with improved BCVA, retinal lesion size, and vitreous inflammation reported in both groups. Overall, 28 cases (87.5%) in the intravitreal group received one injection and four cases (12.5%) received two injections.

In our study, TRC resolved with a mean interval of 2.48 ± 1.03 weeks, similar to previous reports. Twelve patients required a single intravitreal injection of clindamycin and dexamethasone for disease control and four required two injections. Therefore, the total number of injections required in this study was fewer than reported numbers in the majority of previous reports ranging from two to six injections[11,22,24] and similar to the number of injections required in a trial with comparable inclusion criteria[25].

Recurrence was observed in one patient who responded to a repeated intravitreal injection. No other cases of recurrence were observed during the follow-up period. Similar results were reported by Soheilian *et al.*[25] who observed single episodes of recurrence in four eyes (two in each group) during the follow-up period of at least 2 years.

Intravitreal injections were well tolerated in this study and were not associated with complications during or after the procedure. One eye developed cataract progression, a common complication of ocular inflammatory disease, during the follow-up period. The safety of intravitreal administration of clindamycin and dexamethasone has been reported by a number of studies[10,11,22-26]. Only one case report has documented a case of hypersensitivity reaction, presenting as a generalized erythematous rash following intravitreal clindamycin, in a patient with ocular toxoplasmosis[27].

Despite the limitations of our study, which include a small sample size, short follow-up, period, and lack of a control group, our findings suggest that intravitreal clindamycin and dexamethasone may represent a viable treatment option in patients with active TRC and intolerance, contraindications, or inadequate responses to oral medications. Further studies in the form of randomized, controlled, comparative trials are warranted to evaluate the safety and efficacy of local treatment of ocular toxoplasmosis with intravitreal injections of clindamycin and dexamethasone.

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