

Triamcinolone acetonide induces sterile endophthalmitis in patients with intermediate uveitis: A case report series

MARIUS CRISTIAN ȘUȚĂ^{1*}, OLIMPIU LADISLAU KARANCSI^{2*}, OVIDIU MUȘAT³, NICOLAE BALICA⁴, IASMINA YASAR⁵, COSMIN ROȘCA⁶, SIMONA STANCA⁷ and DIANA-MARIA DĂRĂBUȘ^{1*}

Departments of ¹Ophthalmology and ²Oral Implantology and Prosthetic Restorations on Implants, ‘Victor Babeș’ University of Medicine and Pharmacy, 300041 Timișoara; ³Department of Ophthalmology, ‘Dr. Carol Davila’ Central Military Emergency University Hospital, 010825 Bucharest; ⁴Department of ENT, ‘Victor Babeș’ University of Medicine and Pharmacy; ⁵Department of Ophthalmology, Timișoara County Emergency Clinical Hospital, 300041 Timișoara; ⁶Department of Ophthalmology, Oculens Clinic, 400501 Cluj-Napoca; ⁷Department of Pediatrics, ‘Carol Davila’ University of Medicine and Pharmacy, 020021 Bucharest, Romania

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Abstract. Due to their anti-inflammatory, antiangiogenic and antiedematous properties, corticosteroids have been commonly used in the treatment of retinal diseases. Intravitreal administration of steroids offers the maximal drug efficacy and the lowest risk of systemic side effects. The authors report three cases of presumed sterile endophthalmitis induced by triamcinolone acetonide (TA) in three eyes with intermediate non-infectious uveitis. Each patient received a single intravitreal injection of TA of 4 mg. Because of the intense vitreous inflammatory reaction, retina examination and the optical coherence tomography could not be performed, although vitreous opacities were observed on the ocular ultrasound. The dense vitreous opacity is a defining factor, the anterior segment inflammation is mild to moderate and a hypopyon is present, which may be a sterile inflammatory reaction or the triamcinolone material itself. In cases of sterile endophthalmitis, the visual acuity increases progressively as the intraocular inflammation diminishes. Local treatment with topical antibiotics, prednisolone acetate and cycloplegic eyedrops is recommended to control the inflammatory reaction.

Introduction

Corticosteroids can effectively control intraocular inflammation in patients with uveitis. Intraocular inflammation in uveitis causes vitreous opacity, retinal exudates, retinal haemorrhages, serous detachment, retinal neovascularization and cystoid macular edema (1,2). Corticosteroids have been used since 1950 for the treatment of ocular inflammatory diseases (3). They have anti-inflammatory, antiangiogenic, and anti-permeability properties that make them a viable therapeutic option for a range of posterior segment diseases. The reduction of exudation, the stabilization of the blood-retinal barrier and the downregulation of inflammatory stimuli are among the main effects of steroids, even though the specific mechanisms remain unexplained. Steroids act by induction of proteins called lipocortins, in particular phospholipase A2. The proteins have multiple roles, such as the reduction of leukocyte chemotaxis, the control of biosynthesis, and the inhibition of arachidonic acid release from the phospholipid membrane. The arachidonic acid represents the most important precursor of potent inflammatory cell mediators, such as prostaglandins and leukotrienes. This regulation influences the expression of vascular endothelial growth factors (VEGF), inhibits pro-inflammatory genes, such as tumor necrosis factor-alpha (TNF- α) and other inflammatory chemokines, and induces the expression of anti-inflammatory factors, such as pigment-derived growth factor (PEDF) (4,5). Moreover, steroids seem to reduce the expression of matrix metalloproteinases (MMPs) and to downregulate intercellular adhesion molecule 1 (ICAM-1) on choroidal endothelial cells (6).

Several routes of administration have been considered for the treatment of various ocular diseases. Direct injection through the pars plana leads the steroids to the vitreous cavity. Many authors have suggested and reported that local intravitreal delivery of steroids inhibits proliferation of cells, intraocular inflammation and neovascularization (7).

Correspondence to: Dr Olimpiu Ladislau Karancsi, Department of Oral Implantology and Prosthetic Restorations on Implants, ‘Victor Babeș’ University of Medicine and Pharmacy, Piața Eftimie Murgu 2, 300041 Timișoara, Romania
E-mail: olilk@yahoo.com

*Contributed equally

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By using the intravitreal delivery method, the adverse systemic side effects of steroids are avoided. Intravitreal steroid path bypasses the blood-retinal barrier, leading to a more concentrated dose of steroids for a longer period of time. Considering the autoimmune nature of uveitis, patients should be tested for associated diseases before administering intraocular steroids (8-12). In order to exclude an infectious cause of uveitis, general examination and blood tests should be performed (13-18).

Triamcinolone acetonide (TA) belongs to the glucocorticoid family. It is a synthetic steroid with a fluorine in the ninth position and it is the most used steroid agent for the treatment of several retinal conditions (19). TA has an anti-inflammatory potency five times higher than hydrocortisone, with a tenth of the sodium-retaining potency. Its presentation form is a white colored crystalline powder insoluble in water, which explains its prolonged duration of action (20). Its therapeutic effects last approximately three months after 4 mg intravitreal TA injection (21). A longer anti-inflammatory effect can be obtained with slow-release intravitreal dexamethasone implants, but it is also associated with a higher complication rate (cataract formation, elevated intraocular pressure, retinal detachment) (22). In some cases, the intraocular pressure can become refractory to treatment and very difficult to manage (23,24).

Case reports

The authors report three cases where TA induced presumed sterile endophthalmitis in three eyes with intermediate uveitis. All three patients presented decreased visual acuity, blurry vision and floaters in the right eye. A baseline clinical examination was performed, including best-corrected visual acuity (BCVA), biomicroscopy of the anterior pole, intraocular pressure (IOP) and ocular ultrasound. Fundus examination and optical coherence tomography could not be performed because of the vitreous haze.

Case 1: 18-year-old female, BCVA right eye = 0.4 (20/50), left eye = 1 (20/20), IOP = 16 mmHg, normal aspect of the anterior pole, vitreous haze evenly localized of 3+, corresponding to moderate inflammation (25). The inflammatory reaction was observed on the ocular ultrasound (Fig. 1A).

Case 2: 35-year-old male, BCVA right eye = 0.3 (20/63), left eye = 1 (20/20), IOP = 18 mmHg, normal aspect of the anterior pole, vitreous haze evenly localized of 4+, corresponding to marked inflammation (25). The inflammatory reaction was observed on the ocular ultrasound (Fig. 2A).

Case 3: 42-year-old male, BCVA right eye = 0.1 (20/200), left eye = 1 (20/20), IOP = 12 mmHg, normal aspect of the anterior pole, vitreous haze evenly localized of 4+, corresponding to marked inflammation (25). The ultrasound revealed the inflammatory reaction (Fig. 3A).

Each patient received a single intravitreal injection of 4 mg TA. All injections were performed in the operating theatre. After topical disinfection with povidone-iodine, the sterile field and the lid speculum were applied. Local anesthesia with 0.4% oxybuprocaine drops was performed and local antibiotic drops were spread on. Injections were performed using 30 gauge needles through the inferotemporal pars plana, 4 mm from the limbus.

The present study was approved by the local Ethics Committee of the 'Centrul Oftalmologic Prof. Dr. Munteanu' Clinic (Timisoara, Romania). Signed written informed consents were obtained from the patients. All patients expressed in writing, prior to the treatment, their informed consent to receive intraocular treatment with triamcinolone acetonide.

Results and Discussion

After 24 h, each of the patients came to our clinic and reported a decline in their visual acuity. After performing the ocular examinations, we concluded that all three patients had developed an acute sterile inflammatory reaction to TA, called sterile endophthalmitis, in their right eye.

Case 1: 24 h after the injection, BCVA right eye = 0.1 (20/200), left eye = 1 (20/20), normal IOP, anterior chamber flare 2+, vitreous haze evenly localized of 4+, corresponding to marked inflammation (25). The increased inflammatory reaction was also observed on the ultrasound (Fig. 1B).

Case 2: 24 h after the injection, BCVA right eye = counting fingers, left eye = 1 (20/20), normal IOP, anterior chamber cells 3+, vitreous haze evenly localized of 5+, corresponding to severe inflammation (25). The increased inflammatory reaction was also observed on the ocular ultrasound (Fig. 2B).

Case 3: 24 h after the injection, BCVA right eye = hand motion, left eye = 1 (20/20), normal IOP, anterior chamber 0.2 mm pseudo-hypopyon, vitreous haze evenly localized of 5+, corresponding to severe inflammation (25). The increased inflammatory reaction was also noted on the ultrasound (Fig. 3B).

All patients received local treatment with topical antibiotics, prednisolone acetate and cycloplegic eye drops; the vitreous inflammation resolved within 3 weeks in the first case and within 4 weeks in the other two cases. Our conclusion that these were cases of sterile, rather than infectious endophthalmitis was based on the resolution of the inflammation without the use of intravitreal antibiotics.

The causes of sterile endophthalmitis are not entirely understood. Some authors have suggested that the contamination of triamcinolone vials with endotoxins might be a possible cause, but studies performed on vials of triamcinolone showed no endotoxins (26,27). Other researchers have mentioned a toxic effect of the triamcinolone itself, as well as the preservatives present in the vial (benzyl alcohol, polysorbate 80 and carboxymethylcellulose sodium) (28).

In a previous report, Lam *et al* (29) debated the issue of whether sterile endophthalmitis after intravitreal triamcinolone injection is a result of the preservatives contained in the triamcinolone suspension. In both cases described in this study, patients were injected with preservative-free triamcinolone and they developed presumed non-infectious endophthalmitis despite the absence of preservatives. The situation was similar to ours, since we used preservative-free triamcinolone in all eyes. Allergic reactions to triamcinolone have been described, but they were most likely due to preservatives (30).

There are two kinds of potential complications of intravitreal corticosteroid treatment: one is steroid-related and

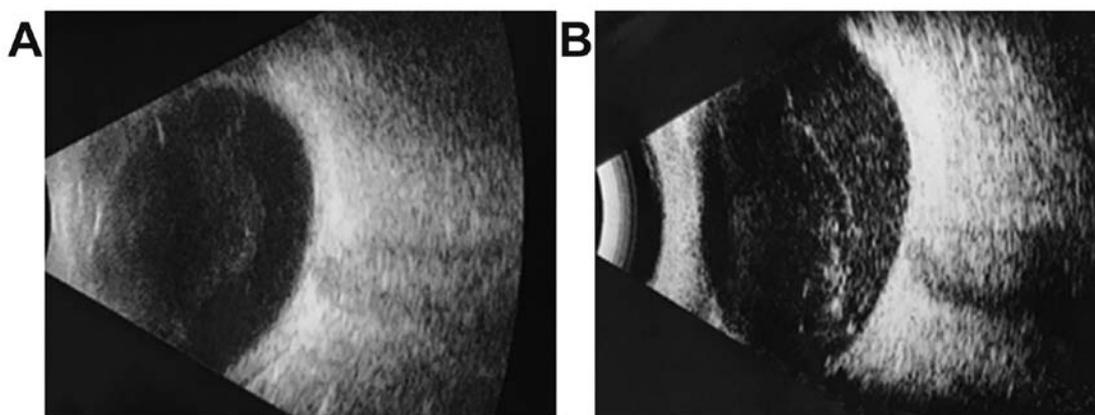


Figure 1. Case 1, ultrasound aspect of the right eye. (A) Before intraocular treatment. (B) One day after the intraocular treatment.

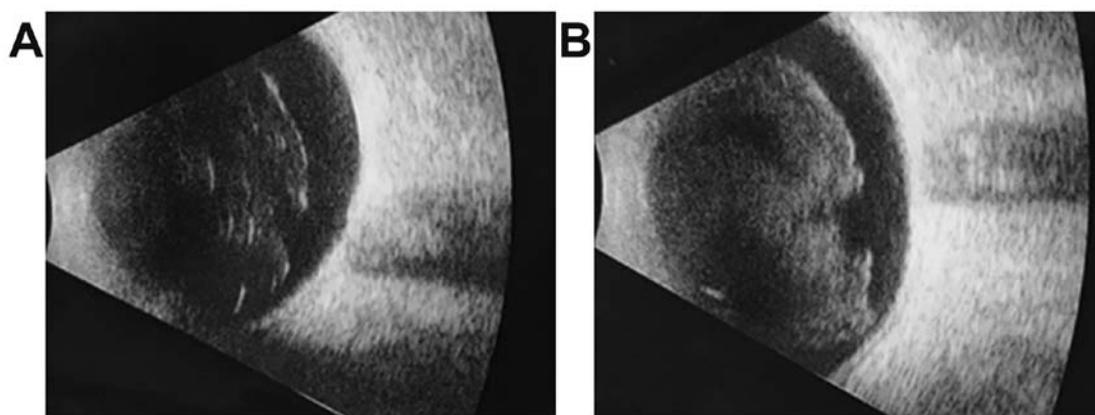


Figure 2. Case 2, ultrasound aspect of the right eye. (A) Before intraocular treatment. (B) One day after the intraocular treatment.

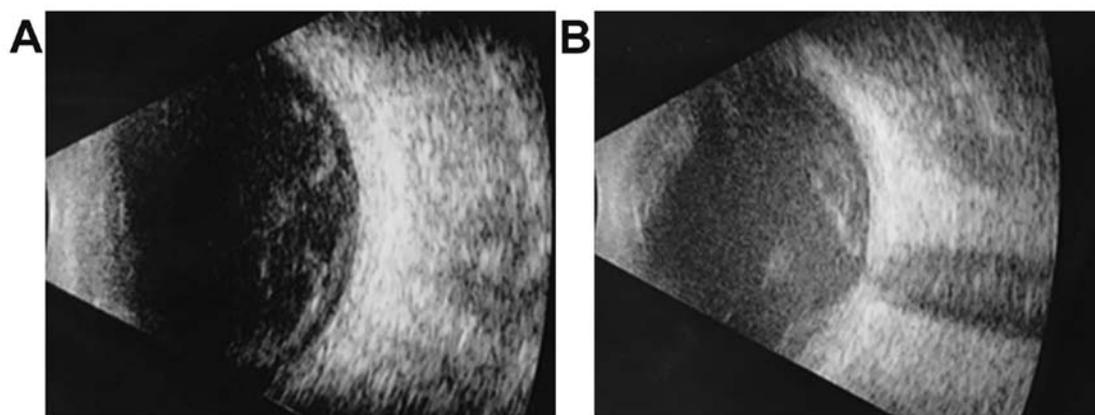


Figure 3. Case 3, ultrasound aspect of the right eye. (A) Before intraocular treatment. (B) One day after the intraocular treatment.

the other one is injection-related adverse effects. Cataract formation and an intraocular pressure increase refer to steroid-related side effects. Injection-related adverse effects include infectious endophthalmitis, sterile endophthalmitis and retinal detachment (31).

In conclusion, the severe inflammatory reaction, named sterile endophthalmitis, which appears after the intravitreal administration of triamcinolone in patients with uveitis,

seems to occur mainly in the context of the off-label use of anti-inflammatory drugs that have not been approved for intravitreal use, most cases presenting a painless and acute vision loss. If the ophthalmologist is not sure about the sterile origin of the inflammation, this complication must be treated as an acute endophthalmitis because of the severe visual outcome of this intraocular infection without antibiotic therapy. The aetiology of sterile endophthalmitis, regardless of the intravitreal

drug used, remains uncertain and a multifactorial origin must be considered.

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Availability of data and materials

All data generated or analyzed during the study are included in this published article.

Authors' contributions

MCȘ conceived and designed the study, and was responsible for the acquisition of the data. OLK, NB and SS were involved in the design of the study and revised the manuscript. OM, CR, IY and DMD were also involved in the conception and design of the study, and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the local Ethics Committee of the 'Centrul Oftalmologic Prof. Dr. Munteanu' Clinic (Timisoara, Romania).

Patient consent for publication

Signed written informed consents were obtained from the patients. All patients expressed in writing, prior to the treatment, their informed consent to receive intraocular treatment with triamcinolone acetonide.

Competing interests

The authors declare that they have no competing interests.

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