Noninfectious Endophthalmitis Associated With Intravitreal Triamcinolone Injection

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Background: Intravitreal injection of triamcinolone has been advocated to treat exudative macular diseases such as macular edema and choroidal neovascularization.

Objective: To describe 7 patients who developed a clinical picture simulating endophthalmitis after intravitreal triamcinolone injection.

Methods: Intravitreal triamcinolone injections were performed to treat refractory cystoid macular edema or diffuse macular edema associated with diabetic retinopathy, macular pucker, branch retinal vein occlusion, or pseudophakia. One patient received an injection in an attempt to treat exudation associated with occult choroidal neovascularization.

Results: Preinjection visual acuity ranged from 20/50 to 20/400. An extensive inflammatory response developed 1 to 2 days after injection in all 7 eyes. Five eyes had previously undergone vitrectomy. Four eyes had a layered hypopyon. All 7 eyes had an anterior chamber cellular reaction and vitritis. Visual acuity ranged from 20/400 to hand movements. The first 6 patients were treated for presumed endophthalmitis with vitreous cultures and intravitreal injections of antibiotics. All 6 cultures were negative for any organisms, and the eyes resolved their inflammatory response, with recovery to preinjection visual acuity or better. The seventh patient was treated with topical prednisolone without antibiotic therapy, and the inflammation resolved, with resolution of the macular edema seen before the intravitreal triamcinolone injection.

Conclusion: It may be appropriate to closely observe noninfectious, toxic endophthalmitis in patients treated with intravitreal triamcinolone before assuming it to be infectious, especially in the absence of eye pain.

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Cystoid macular edema (CME) is a common cause of compromised central vision and is associated with numerous coexisting conditions. Initial treatment depends on the underlying cause and includes topical or periocular corticosteroids and nonsteroidal anti-inflammatory medications. In cases associated with diabetic macular edema and vascular occlusions, local laser treatment is often indicated. In cases of an associated macular pucker or vitreomacular traction, vitrectomy with membrane peeling is necessary.

However, despite using the previously mentioned therapeutic modalities, many patients have persistent CME. Corticosteroids inhibit prostaglandin and leukotriene synthesis, thereby inducing an anti-inflammatory effect. Furthermore, corticosteroids reverse capillary permeability, stabilizing blood vessels and the blood-retinal barrier. Intravitreal triamcinolone acetonide has recently been shown to be nontoxic to the human retina and well tolerated, and it has been advocated recently as treatment for refractory CME. Intravitreal triamcinolone is also a potential therapy for choroidal neovascularization associated with age-related macular degeneration, as it decreases capillary permeability and reduces subretinal fluid exudation.

As with any therapeutic modality, the benefits must be weighed against the risks. The most common risks associated with intraocular corticosteroid therapy are elevation of intraocular pressure and progression of cataract. The risk of endophthalmitis exists with any intraocular injection or penetration. We describe 7 patients who developed a clinical picture simulating endophthalmitis after intravitreal triamcinolone injection that we believe represents a toxic reaction to the material injected.

METHODS

Intravitreal triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, Princeton, NJ) in-
Recurrence for the treatment of refractory CME or occult choroidal neovascularization has been used as a treatment modality by us since May 2001. The risks and benefits of the procedure were discussed with and written informed consent was obtained from each patient before injection. The eye was prepared with povidone-iodine (Betadine; Purdue Frederick Co, Norwalk, Conn) (5% or 10%) solution and ciprofloxacin hydrochloride (Ciloxan; Alcon Inc, Ft Worth, Tex) drops to obtain sterile conditions. A sterile wire lid speculum was placed in the eye, and sterile topical or subconjunctival lidocaine hydrochloride was used to anesthetize the inferotemporal quadrant of the eye to be injected.

The triamcinolone was injected inferotemporally through the pars plana using a 30-gauge needle on a 1-mL syringe. In 4 eyes, 1 mg of drug was injected from a new, sterile bottle of triamcinolone acetonide, 40 mg/mL, in a volume of 0.1 mL. In 3 eyes, 4 mg of drug was injected from a new, sterile bottle of triamcinolone acetonide, 40 mg/mL, in a volume of 0.1 mL. The suspension was shaken vigorously before drawing it into the syringe to ensure the correct concentration. The supernatant was not removed, and the drug was not resuspended in other diluent. Patients were instructed to instill ciprofloxacin drops for 2 days after injection, and they returned for a follow-up examination either 1 or 2 days after the procedure.

Between May 1, 2001, and June 30, 2002, we performed 104 intravitreal injections to treat cystoid or diffuse diabetic macular edema that did not respond to focal laser photocoagulation; CME associated with retinal vein occlusions, pseudophakia, or preretinal gliosis; and choroidal neovascularization. We encountered 7 cases of atypical inflammation simulating endophthalmitis after triamcinolone injection, all occurring between January 16, 2002, and February 19, 2002.

### RESULTS

Four women and 3 men were identified as having a clinical picture simulating endophthalmitis after intravitreal triamcinolone injection (mean age, 67 years; range, 37–84 years). All 7 eyes had previously undergone intraocular surgery. Five eyes were pseudophakic, and 5 eyes had previously undergone vitrectomy (Table 1). Intravitreal triamcinolone injections were performed to treat cystoid or diffuse diabetic macular edema that did not respond to focal laser photocoagulation in 3 eyes, CME associated with a mild macular pucker or with a branch retinal vein occlusion in 1 eye each, pseudophakic CME after a secondary anterior chamber intraocular lens in 1 eye, and exudation associated with choroidal neovascularization in 1 eye.

The dose of triamcinolone injected was either 1 or 4 mg. In patients with their first injection for treatment of CME, 1 mg was typically administered. For patients with an incomplete response to a previous injection or recurrent macular edema after an excellent response to a previous injection, 4 mg was injected. For patients with choroidal neovascularization, 4 mg was administered. Patient 7 is an exception in that he received a 4-mg injection for diabetic CME without any previous intravitreal corticosteroid treatment.

Preinjection visual acuity ranged from 20/50 to 20/400. All 7 eyes had acute, painless loss of vision on the first visit after intravitreal injection. Visual acuity after injection ranged from 20/400 to hand movements. Three patients were examined 1 day after injection, and the other 4 were seen 2 days after injection. An extensive inflammatory response was observed in all 7 patients, with anterior chamber cell and flare and posterior segment vitritis (Table 2). The response was distinct from triamcinolone suspension particles. In the 4 eyes with hypopyon, the collection in the angle was distinguished from triamcinolone suspension particles, even in pseudophakic eyes, by its appearance and slightly yellow color. The vitritis obscured the fundus details in all 7 eyes; however, in 4 eyes, the inflammation was so extensive that B-scan ultrasonography was necessary to evaluate the retina, as only the red reflex was visible. B-scan ultrasonography in these cases revealed dense vitritis without retinal detachment.

The first 6 patients were treated for presumed infectious endophthalmitis; they underwent vitreous culture and injection of intraocular antibiotics. Each of these 6 eyes received 1 mg of vancomycin hydrochloride and 2 mg of ceftazidime by intravitreal injection through the pars plana. Four of the vitreous samples were obtained using a vitreous cutter and 2 were obtained via needle aspiration. All vitreous cultures had adequate samples and were plated on blood, chocolate, and Sabouraud agar and on thioglycolate broth. Initial gram stains were not performed routinely. None of the samples were positive for any organisms on these media, and all were thought to be sterile. Owing to a concern that the vials of triamcinolone carried infectious organisms, 3 of the bottles used for injection were cultured. One culture was positive for a presumed contaminant colony of *Staphylococcus aureus* on blood and chocolate agar, and the other 2 were negative. The lot numbers of the triamcinolone vials used for intravitreal injection were recorded, and samples of each lot number were sent for routine culture; all were negative for any organisms.

### Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Diagnosis</th>
<th>Lens Status</th>
<th>Dose of Triamcinolone Injected, mg</th>
<th>Previous PPV</th>
<th>Previous Intraocular Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>DME/CME</td>
<td>Phakic</td>
<td>1</td>
<td>Yes</td>
<td>Yes (60 d earlier)</td>
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<tr>
<td>2</td>
<td>73</td>
<td>DME/CME</td>
<td>Phakic</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>84</td>
<td>Pseudophakic CME</td>
<td>ACIOL</td>
<td>1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>CME with ERM</td>
<td>PCIOL</td>
<td>1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>CME with BRVO</td>
<td>PCIOL</td>
<td>4</td>
<td>Yes</td>
<td>Yes (32 d earlier)</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>CNVM</td>
<td>PCIOL</td>
<td>4</td>
<td>No</td>
<td>Yes (23 d earlier)</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>DME/CME</td>
<td>PCIOL</td>
<td>4</td>
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<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: BRVO, branch retinal vein occlusion; CNVM, choroidal neovascular membrane; DME, diabetic macular edema; CME, cystoid macular edema; ERM, epiretinal membrane; ACIOL, anterior chamber intraocular lens; PCIOL, posterior chamber intraocular lens; PPV, pars plana vitrectomy.
Patient 7 had a similar clinical picture of endophthalmitis but was observed closely and was treated with topical prednisolone acetate without topical, intracocular, or systemic antibiotic therapy. The inflammation improved in the initial 2 days and resolved completely during the ensuing 3 weeks, with disappearance of all vitritis and absence of the preexisting macular edema. Visual acuity improved from 20/200 before triamcinolone injection to 20/70 afterward.

In the other 5 eyes with macular edema (patients 1-5), the CME resolved completely in 3 and was reduced on fluorescein angiography in the other 2, despite developing endophthalmitis and undergoing further intervention. The patient with choroidal neovascularization associated with age-related macular degeneration was later enrolled in a clinical trial that involved intravitreal injections of an inhibitor of vascular endothelial growth factor. She mounted a similar inflammatory response to this injection, but her inflammation resolved without sequelae and her visual acuity improved from an initial baseline value of 20/200 to 20/60, with a substantial decrease in subretinal fluid exudation.

### Table 2. Clinical Findings

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Visual Acuity Before Injection</th>
<th>Examination After Injection, d</th>
<th>AC Reaction (Range, 0-4)</th>
<th>Hypopyon</th>
<th>Vitritis (Range, 0-4)</th>
<th>Cultures</th>
<th>Final Visual Acuity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/300</td>
<td>20/400</td>
<td>2</td>
<td>1+</td>
<td>No</td>
<td>4+</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>20/400</td>
<td>1/200</td>
<td>2</td>
<td>1+</td>
<td>No</td>
<td>2+</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>20/200</td>
<td>2/200</td>
<td>1</td>
<td>3+</td>
<td>Yes</td>
<td>3+</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>20/400</td>
<td>HM</td>
<td>2</td>
<td>4+</td>
<td>Yes</td>
<td>4+</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>20/50</td>
<td>HM</td>
<td>1</td>
<td>4+</td>
<td>Yes</td>
<td>3+</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>20/200</td>
<td>HM</td>
<td>1</td>
<td>4+</td>
<td>Yes</td>
<td>4+</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>20/200</td>
<td>HM</td>
<td>2</td>
<td>3+</td>
<td>No</td>
<td>4+</td>
<td>Not performed</td>
</tr>
</tbody>
</table>

Abbreviations: AC, anterior chamber; HM, hand movements.

**COMMENT**

Intravitreal triamcinolone injections have been associated with reductions in capillary permeability and resolution of macular edema in patients with CME with multiple causes. Patients with choroidal neovascularization may benefit from intracocular corticosteroid therapy owing to the reduction in subretinal fluid exudation and from the bacteriostatic effect of triamcinolone. However, any invasive intervention has risks. The most common adverse effects of intravitreal triamcinolone injection are a transient elevation in intraocular pressure and potential worsening of a cataract. Although endophthalmitis is an obvious potential adverse effect of intravitreal injections, it is extremely rare when appropriate sterile technique is practiced. In our review of 104 cases of intravitreal triamcinolone injection, we found 7 cases of endophthalmitis clustered between January 16, 2002, and February 19, 2002. We believe that these cases represent noninfectious endophthalmitis—probably a toxic reaction to the drug, the vehicle in which it is suspended, or a contaminant in the vials involved in this series.

The basis of this assumption derives from multiple facts. (1) All 6 cases that were cultured failed to reveal organisms, and the 1 eye that was observed resolved spontaneously without antibiotic therapy. No cases of culture-positive endophthalmitis have been seen since we began using this therapeutic modality. (2) All 7 cases presented acutely without pain, whereas infectious endophthalmitis typically manifests acutely or subacutely with pain. (3) All 7 patients rapidly recovered to their preinjection levels of visual acuity, typically within days of developing endophthalmitis, suggesting a toxic reaction to the dose of injected material. Most of the patients even recovered to better visual acuity owing to resolution of the macular edema.

All 7 patients experienced severe inflammation within 2 days of intravitreal injection. If a patient develops new symptoms more than several days after injection, infectious endophthalmitis should be presumed and immediate therapy should be initiated.

Many patients in this series were pseudophakic or had previously undergone vitrectomy (n=5 [71%] for both). It is possible that in eyes that have not undergone vitrectomy, the drug remains more sequestered in the vitreous cavity, diffusing more slowly to the intraocular structures. In eyes that have undergone vitrectomy, the drug has direct access to the ocular coats, allowing any toxic agent to more readily induce a brisk immune response. Similarly, in patients with pseudophakia, the relative unicameral nature of the eye may allow for a more robust immune response.

Furthermore, many patients developed endophthalmitis after receiving a second injection of triamcinolone (n=4 [57%]). It is possible that the eye is more likely to mount an immune response when receiving a second injection, especially if less than 6 weeks has elapsed since the previous injection.

We did not pinpoint a specific lot number or type of triamcinolone packaging (10 mg/mL, 1-mL vials; 40 mg/mL, 5-mL vials; or 40 mg/mL, 1-mL vials) that was more suspect because these endophthalmitis cases represent varied lot numbers and were administered from all 3 types of newly opened triamcinolone vials. The clustering of cases in a 5-week period raises the suspicion that some toxin existed in the vial that prompted susceptible patients to mount an inflammatory reaction. No modification of the intravitreal injection technique was noted during this period that could explain the incidence of severe inflammation or endophthalmitis. After these cases were noted, we returned all our held stock

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of triamcinolone to the manufacturer in exchange for new vials, and we have not encountered any other cases of endophthalmitis.

Infectious endophthalmitis can occur after intravitreal triamcinolone injection, with potentially devastating adverse effects, and it is possible that intraocular corticosteroid use blunts the usual ability of the eye to eradicate infectious organisms. However, we believe that in select eyes injected with triamcinolone under sterile conditions, the differential diagnosis includes a sterile, toxic endophthalmitis that may be appropriate to observe closely, perhaps every 8 to 12 hours, to determine whether the inflammation is worsening or improving. Some patients who do not require further surgery can avoid unnecessary intervention and clear their inflammation spontaneously.

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REFERENCES