Use of Voriconazole in the Surgical Management of Chronic Postoperative Fungal Endophthalmitis

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ABSTRACT
Management of postoperative mycotic endophthalmitis remains challenging. This study reports successful management of postoperative chronic fungal endophthalmitis with vitrectomy surgery and voriconazole. A retrospective interventional case series of four eyes of four patients with chronic fungal endophthalmitis treated with pars plana vitrectomy and oral and intravitreal voriconazole is described. Pars plana vitrectomy, en bloc capsulectomy, and explantation of the intraocular lens were then performed combined with one to four intravitreal injections of voriconazole and oral voriconazole for up to 5 weeks. Identified fungal species included Aspergillus, Acremonium, Penicillium, and Verticillium. Voriconazole may have affected the clinical and surgical management of fungal endophthalmitis. [Ophthalmic Surg Lasers Imaging 2009;40:425-431.]

INTRODUCTION
Management of mycotic endophthalmitis remains challenging. Delayed diagnosis and identification of the involved microorganism combined with the limited profile of available antifungal agents influence the dreadful prognoses of many of these cases. Voriconazole is a novel and potent antifungal triazole agent that has been recently used to treat mycotic endophthalmitis by systemic or intravitreal injection. This article describes four cases of chronic fungal endophthalmitis after cataract surgery that were successfully managed with pars plana vitrectomy and voriconazole administered by oral and intravitreal routes.

We retrospectively reviewed the medical records of four patients who were referred to a reference retina clinic in Minas Gerais, Brazil, between 2003 and 2006 for suspected chronic fungal endophthalmitis presenting after cataract surgery. Culture confirmed fungal etiology in the four cases.

Data collection included a detailed medical history, with emphasis on the ocular disease and previous treatments. Records of the ophthalmic examination of the four patients were also analyzed, including best-corrected visual acuity, biomicroscopy of the anterior segment, indirect ophthalmoscopy, and the results of further examinations at presentation and during follow-up.

The four cases did not have a favorable response to intravitreal amphotericin B; two had previously received the drug and two were treated soon after admission. All patients underwent pars plana vitrectomy, including en bloc capsulectomy and intraocular lens explantation in three cases (the remaining case had already undergone it), as well as treatment with oral voriconazole (200 mg twice daily for a variable period) and between one and four intravitreal injections of 100 to 200 μg of voriconazole through the temporal inferior pars plana. Corticosteroid use was avoided or suspended as soon as the fungal infection was confirmed by culture.

Table 1 summarizes the main data of these cases.

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Accepted for publication June 17, 2008.
The authors have no financial or proprietary interest in the materials presented herein.
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do: 10.3928/15428877-20090630-16.

CASE REPORT
### Table 1: Summary of Four Cases of Chronic Fungal Endophthalmitis After Cataract Surgery Treated With Voriconazole

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>50</td>
<td>67</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Initial BCVA</td>
<td>20/150</td>
<td>20/150</td>
<td>Hand motions</td>
<td>20/30</td>
</tr>
<tr>
<td>Final BCVA</td>
<td>20/800</td>
<td>20/800</td>
<td>20/30</td>
<td>20/40</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>Pars plana vitrectomy + capsulectomy; IOL explantation</td>
<td>2 pars plana vitrectomies*</td>
<td>Pars plana vitrectomy + capsulectomy; IOL explantation</td>
<td>Pars plana vitrectomy + capsulectomy; IOL explantation</td>
</tr>
<tr>
<td>Antifungal treatment</td>
<td>2 IV-VCZ; oral voriconazole</td>
<td>4 IV-VCZ + amphotericin B; oral voriconazole</td>
<td>1 IV-VCZ; oral voriconazole</td>
<td>1 IV-VCZ; oral voriconazole</td>
</tr>
<tr>
<td>Isolate</td>
<td>Aspergillus sp</td>
<td>Pénicillium sp</td>
<td>Verticillium sp</td>
<td></td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; IOL = intraocular lens; IV-VCZ = intravitreal voriconazole injection.

*IOL and posterior capsule had already been removed in a former pars plana vitrectomy.

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**Case Reports**

**Case 1**

A 50-year-old man was referred due to suspicion of mycotic endophthalmitis. Visual acuity had decreased 3 weeks after clear corneal phacoemulsification with intraocular lens implantation in his right eye. He then underwent pars plana vitrectomy and intravitreal injection of vancomycin. Because vitreous sampling yielded *Aspergillus flavus*, an intravitreal injection with amphotericin B was performed 2 months after cataract surgery. He had been prescribed ketoconazole for 15 days.

At presentation, he was receiving topical prednisolone acetate and amikacin. Initial best-corrected visual acuity was 20/150 in the right eye and 20/25 in the left eye. Biomicroscopy of the right eye showed moderate conjunctival injection, 1+/4+ flare, 2+/4+ cells in the anterior chamber, a hypopyon, and whitish deposits on the intraocular lens surface (Fig. 1). Intraocular pressure was normal. Examination of the left eye was unremarkable.

Considering the failure of previous treatment, re-operation with pars plana vitrectomy, en bloc capsulectomy, intraocular lens explantation, and intravitreal injection of voriconazole (133 µg) were performed. Oral voriconazole (200 mg twice daily for 5 weeks) and diclofenac combined with topical ciprofloxacin and atropine were prescribed. Despite this treatment, there was a slow progressive worsening of the inflammatory reaction. Two weeks later, a second intravitreal injection of voriconazole (200 µg) was necessary. Inflammatory reaction then gradually ceased. At 12 weeks, final best-corrected visual acuity was 20/800 due to a tractional retinal detachment involving the macula.

**Case 2**

A 67-year-old woman with diabetes mellitus presented with chronic endophthalmitis in the right eye of 3 months' duration that began 2 weeks after uneventful clear corneal phacoemulsification with intraocular lens implantation. She underwent an initial pars plana vitrectomy and later a second pars plana vitrectomy with en bloc capsulectomy, intraocular lens explantation, and three intravitreal injections of amphotericin B were needed. Vitreous cultures had been negative.

At presentation, best-corrected visual acuity was...
20/150 in the right eye and 20/25 in the left eye. Biomicroscopy of the right eye revealed mild conjunctival hyperemia, 1+/4+ cells in the anterior chamber, and a filamentous whitish mass in the anterior chamber covering the iris at the 10-o’clock position (Fig. 2). Ophthalmoscopy showed macular pucker in this eye.

A pars plana vitrectomy with removal of the whitish mass and an extensive excision of the fibrotic tissue behind the iris, epiretinal membrane peeling, and intravitreal injection of voriconazole (200 μg) and vancomycin were performed. Oral voriconazole (200 mg) twice daily was prescribed. As the inflammatory reaction increased, reoperation with pars plana vitrectomy and a second intravitreal injection of voriconazole (200 μg) and amphotericin B were scheduled. A third and fourth intravitreal injection of voriconazole (200 μg) and amphotericin B were administered 1 and 2 weeks, respectively, thereafter. Vitreous cultures revealed Acremonium species. Oral voriconazole (200 mg) twice daily was maintained for 5 weeks.

One week after the last injection, a choroidal detachment was detected. In the following week, a retinal detachment with severe (CP7A6) proliferative vitreoretinopathy was also noted. The patient refused surgical treatment. One week later, proliferative vitreoretinopathy became more severe (CP12A12-type 5) and a pars plana vitrectomy with membrane peeling, 360° retinectomy, endolaser treatment, and silicone oil tamponade were performed after the patient gave consent. Inflammatory reaction then gradually improved. Four months later, best-corrected visual acuity was stable at 20/800. Despite chronic hypotony, the retina remained attached with silicone oil and the optic disc was significantly pale 18 months after the last surgery.

Case 3

A 61-year-old woman was referred for chronic endophthalmitis 1 month after clear corneal phacoemulsification with intraocular lens implantation in the left eye. She had been unsuccessfully treated with oral prednisone (40 mg/day), doxycycline, and clindamycin combined with intravitreal vancomycin and ceftazidime.

At presentation, best-corrected visual acuity was hand motions in the left eye and 20/30 in the right eye. Biomicroscopy revealed mild conjunctival injection, subconjunctival hemorrhage, Descemet’s membrane striae, 2+/4+ flare and cells in the anterior chamber, and a fibrinous membrane on the intraocular lens surface (Fig. 3). Ophthalmoscopy was normal in the right eye and not possible in the left eye due to opaque media. Echography (b-scan) of the left eye showed vitreous opacities and posterior hyaloid detachment.

The patient then underwent pars plana vitrectomy with en bloc capsulectomy, intraocular lens explantation, and intravitreal injection of ceftazidime, vancomycin, amphotericin B, and dexamethasone. Vitreous sampling disclosed Penicillium species. An oral course of voriconazole (200 mg twice daily) was prescribed and maintained for 2 weeks. There was an increase in the intraocular inflammation; an intravitreal injection of voriconazole (200 μg) was performed 1 week later with subsequent progressive improvement in inflammatory reaction. The oral voriconazole was maintained...
for 3 weeks. At 6 months, best-corrected visual acuity had improved to 20/30 and was maintained until 19 months of follow-up.

Case 4

A 60-year-old man with insulin-dependent diabetes mellitus presented with clinical suspicion of fungal endophthalmitis. Six months previously, he had undergone an uneventful clear corneal phacoemulsification with intraocular lens implantation in the right eye. In the fifth postoperative week, the right eye presented with a mild decrease in visual acuity and redness soon after Nd:YAG laser capsulotomy. Topical prednisolone acetate and oral fluconazole (150 mg daily) were then used for 3 months.

At presentation, best-corrected visual acuity was 20/30 in the right eye and 20/25 in the left eye. Biomicroscopy of the anterior segment of the right eye disclosed a delicate grayish-white translucent filamentous net in the temporal aspect of the anterior chamber (Fig. 4), sectorial iris atrophy, and a whitish opacity covering the posterior surface of the intraocular lens. The left eye showed incipient lens opacification. Intraocular pressure was normal. Fundus examination revealed treated nonproliferative diabetic retinopathy with microaneurisms and microhemorrhages and sparse pigmented chorioretinal laser-induced scars.

A pars plana vitrectomy and injection of vancomycin, ceftazidime, and amphotericin B were then performed. Vitreous culture allowed isolation of Verticillium species. As inflammation worsened, the patient underwent another pars plana vitrectomy with en bloc capsulectomy, explantation of the intraocular lens, and injection of voriconazole (133 g). Oral voriconazole was also initiated (200 mg twice daily) and maintained for 1 week. Improvement of media clarity and inflammation was observed in the following weeks. Three months after the last surgery, final best-corrected visual acuity was 20/40.

DISCUSSION

Approximately 0.1% of cataract surgeries are complicated by infectious endophthalmitis. Most of the implicated isolates are bacteria, but fungal etiology has been variably uncovered, posing a diagnostic and therapeutic challenge. Fungal endophthalmitis may present in the early or late postoperative period. Our patients had latency from 2 to 5 weeks. In one of them, Nd:YAG laser capsulotomy might have precipitated the onset of symptoms by spreading microorganisms possibly sequestered into the capsular bag, as previously hypothesized.

Possible conditions predisposing to fungal infection include chronic ocular surface disease, contact lens use, prolonged use of topical or systemic steroids, trauma, and absolute or relative immunosuppression due to systemic diseases such as acquired immune deficiency syndrome, renal failure, and diabetes mellitus. Half of the patients studied had diabetes mellitus, which might have facilitated fungal growing. Moreover, it should be noted that all four eyes had undergone phacoemulsification through a clear corneal incision, which is a possible risk factor for endophthalmitis.

Most of the patients had had previous surgical treatment for endophthalmitis, although the lens capsule and intraocular lens had been removed in only one instance. In all, three cases demanded a more aggressive surgical treatment, with extensive pars plana vitrectomy, en bloc capsulectomy, and intraocular lens explantation along with intravitreal and oral voriconazole. This more radical surgical approach has attained the highest cure rates in series of chronic Propionibacterium acnes endophthalmitis following cataract surgery and may also provide higher cure rates in chronic fungal endophthalmitis.
TABLE 2
Summary of Published Reports on Systemic and Intravitreal Use of Voriconazole in Fungal Endophthalmitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Eyes/ Patients</th>
<th>Type/ Etiology of FE*</th>
<th>Routes of Voriconazole Use*</th>
<th>Outcome/ Final BCVAa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott et al., 20049</td>
<td>1/1</td>
<td>Bleb-associated Lecythophora mutabilis</td>
<td>Oral Intravitreal</td>
<td>Cure 20/80</td>
</tr>
<tr>
<td>Nehemy et al., 20064</td>
<td>1/1</td>
<td>Post-cataract surgery Verticillium sp</td>
<td>Oral Intravitreal</td>
<td>Cure 20/40</td>
</tr>
<tr>
<td>Kramer et al., 20065</td>
<td>1/1</td>
<td>Endogenous Aspergillus terreus</td>
<td>Intravenous Oral Intravitreal</td>
<td>Cure 20/50</td>
</tr>
<tr>
<td>Sen et al., 20066</td>
<td>5/5</td>
<td>Post-cataract surgery (3) Endogenous (2) Aspergillus sp (3) Fusarium sp (1) Scedosporium apiospermum (2)</td>
<td>Intravitreal (5) Intracameral (1)</td>
<td>Cure (5) 20/60 (1) 20/120 (1) 20/400 (1) Light perception (2)</td>
</tr>
<tr>
<td>Zarkovic et al., 20077</td>
<td>1/1</td>
<td>Post-traumatic Scedosporium apiospermum</td>
<td>Oral Intravitreal</td>
<td>Cure 20/40</td>
</tr>
<tr>
<td>Aydin et al., 20078</td>
<td>2/2</td>
<td>Post-cataract surgery (2) Aspergillus flavus (1) Scopulariopsis sp (1)</td>
<td>Intravenous (1) Oral Intravitreal (1)</td>
<td>Cure (2) 20/40 (1) CF at 3 meters (1)</td>
</tr>
<tr>
<td>Chen et al., 200719</td>
<td>2/2</td>
<td>Endogenous (2) Scedosporium apiospermum (2)</td>
<td>Intravenous (1) Oral (1) Intravitreal (2)</td>
<td>Failure (2) Enucleation (2)</td>
</tr>
<tr>
<td>Jain et al., 200720</td>
<td>4/3</td>
<td>Endogenous (4) Scedosporium apiospermum (4)</td>
<td>Intravenous (2) Oral (2) Intravitreal (2)</td>
<td>Failure (2) Death (2)</td>
</tr>
<tr>
<td>Moinfar et al., 200721</td>
<td>1/1</td>
<td>Post-traumatic Scedosporium apiospermum</td>
<td>Intravitreal</td>
<td>Failure Enucleation</td>
</tr>
<tr>
<td>Current series, 2009</td>
<td>4/4b</td>
<td>Post-cataract surgery (4) Acremonium sp (1) Aspergillus sp (1) Penicillium sp (1) Verticillium sp (1)</td>
<td>Oral (4) Intravitreal (4)</td>
<td>Cure (4) 20/30 (1) 20/40 (1) 20/800 (2)</td>
</tr>
</tbody>
</table>

FE = fungal endophthalmitis; BCVA = best-corrected visual acuity; CF = counting fingers.

*Number in parentheses refers to the number of eyes.

bOne case did not receive voriconazole.

cOne case was also reported in Nehemy et al. (2006).4

Considering the failure of previous intravitreal injections of amphotericin B, the antifungal of first choice in these cases, we decided to use voriconazole based on its excellent spectrum of activity15,16 and the lack of retinal toxicity in experimental models following intravitreal injection.17,18 However, it was not possible to determine whether clinical failure under amphotericin B was due to fungal resistance because antibiotic susceptibility testing was not available for our cases. Furthermore, in vitro susceptibility to this antibiotic was also not tested for the same fungal isolates despite the favorable clinical response to voriconazole.

Table 2 summarizes published reports on successful3-5,7,8 and unsuccessful19-21 use of intravitreal and oral voriconazole in fungal endophthalmitis. Significant concurrent immunosuppression, fungal virulence, and eventual resistance to voriconazole may have contributed the disappointing outcomes in some cases.19-21 In our series, infection was controlled in all eyes, with two eyes (50%) having wors-
ened final visual acuity to 20/800 (due to a retinal detachment in one eye and optic atrophy in another eye) and the other two eyes achieving good visual acuity (20/30 and 20/40).

Single or multiple doses of intravitreal voriconazole from 10 to 200 µg have been described. Our cases required one to four intravitreal injections of 100 to 200 µg, highlighting that lack of infection control with only one injection does not always indicate a treatment failure in these difficult cases. Many of these challenging cases will need repeated intravitreal injections associated with the systemic antifungal. Experimental studies suggest that intravitreal concentrations of voriconazole up to 25 µg/mL are safe, which would correspond to 100 to 125 µg of the drug into the vitreous cavity of a human eye. Some outer retinal necrosis may occur with vitreous concentrations of voriconazole exceeding 50 µg/mL (200 to 250 µg dose in the human eye). However, in our series and in others, eyes receiving one or multiple intravitreal injections of up to 200 µg of voriconazole did not exhibit any sign of retinal toxicity. In contrast, intravitreal amphotericin B, the current drug of choice for fungal endophthalmitis, seems to have a narrower therapeutic window with a significant risk of intraocular toxicity even with relatively low doses.

As reported in the current study, a course of systemic voriconazole is often used in addition to intravitreal injections of the drug. The half-life of voriconazole after intravitreal injection of 35 µg in the rabbit eye (corresponding to approximately 100 µg injection in the human eye) is approximately 2.5 hours. Even though this period seems to be short, a higher initial dose of intravitreal voriconazole may extend its half-life elimination, allowing a longer exposure to the drug. Moreover, good intraocular penetration of voriconazole following oral or intravenous administration may warrant more prolonged levels required for fungal growth inhibition. In the current series, oral voriconazole was used for up to 5 weeks.

Aggressive surgical management of chronic fungal endophthalmitis following cataract surgery with pars plana vitrectomy, intraocular lens removal, and en bloc capsulectomy associated with intravitreal and oral use of voriconazole may yield good results. Multiple intravitreal injections may be needed. The importance of each one of these procedures seems unclear.

Although not established yet, intravitreal voriconazole may be a good option, especially in cases of treatment failure with amphotericin B, and might become a safer and more efficient alternative with a wider therapeutic window. Large comparative studies are needed to clarify this issue.

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