Successful Treatment of *Fusarium* Keratitis with Cornea Transplantation and Topical and Systemic Voriconazole

Rocus R. Klont,1,4 Cathrien A. Eggink,2 Antonius J. M. M. Rijs,1,4 Pieter Wesseling,3 and Paul E. Verweij1,4

1Departments of Medical Microbiology, 2Ophthalmology, and 3Pathology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

A case of invasive *Fusarium* keratitis in a previously healthy male patient was treated successfully with cornea transplantation and systemic and topical voriconazole after treatment failure with topical amphotericin B and systemic itraconazole. Topical voriconazole was well tolerated, and, in conjunction with the oral administration, it resulted in a high level of the drug in the anterior chamber of the eye (which was 160% of the plasma drug level).

Case report. A previously healthy male, aged 23 years, presented to our hospital (Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands) with severe and very painful keratitis of the right eye, which had developed during 1 week. He used daily-wear, disposable contact lenses and had been diving in the Port of Willemstad, Curacao. The local ophthalmologist in Curacao had started treatment with ciprofloxacin, amphotericin B, acyclovir, and atropine 4 days before the patient presented to our hospital. The visual acuity of the affected eye was limited to hand movements at 1 m. He used daily-wear, disposable contact lenses and had been diving in the Port of Willemstad, Curacao. The local ophthalmologist in Curacao had started treatment with ciprofloxacin, amphotericin B, acyclovir, and atropine 4 days before the patient presented to our hospital. The visual acuity of the affected eye was limited to hand movements at 1 m. The conjunctiva showed severe injection, and a corneal ulcer with an infiltrate measuring 4.5–6.5 mm was present, as was a hypopyon in the anterior chamber of the eye. Direct staining of corneal scrapings showed mycelia, and antifungal treatment was started with a topical amphotericin B 0.5% preparation applied hourly and systemic itraconazole at a dosage of 200 mg administered daily. However, despite this therapy, the infiltrate increased in size and approached the limbal area. Culture of the corneal scrapings grew *Fusarium solani* with an elevated MIC for amphotericin B (4 µg/mL) and itraconazole (>16 µg/mL) but a low MIC for voriconazole (2 µg/mL). The MIC was determined using the microdilution technique according to the NCCLS M38-A guidelines [1]. However, the minimal fungicidal concentration, defined as the lowest concentration at which ≥99.5% of the inoculum is killed, was >16 µg/mL for voriconazole [2]. Penetrating keratoplasty and peripheral iridectomy were performed on day 8 of hospitalization, and medical treatment was changed to intravenous voriconazole (6 mg/kg b.i.d. on the first day, followed by 4 mg/kg b.i.d. on successive days). Because of the rapid progression of the infection, the intravenous formulation of voriconazole was applied topically (as a 1% voriconazole eyedrop solution) at hourly intervals to obtain high drug levels at the site of infection.

Microscopic examination of the resected cornea showed extensive loss of epithelium and a residual Bowman’s membrane (figure 1). An almost complete transmural defect was located centrally, with necrosis in the floor and borders and massive infiltration by neutrophils. Hyphae were detected in the stroma and beneath the residual Bowman’s membrane by use of periodic-acid-Schiff and Grocott staining. Dense accumulations of fungal elements and neutrophils were seen in the floor of the ulceration. The peripheral margins of the excised tissue were free of hyphae. A resected iris fragment also revealed massive infiltration by neutrophils, but fungus was not found in this tissue.

On day 4 after transplantation, dexamethasone 0.1% eye-drops q.i.d. were added to the treatment regimen. *F. solani* grew from the resected cornea and from material from the anterior chamber that was obtained peroperatively. The corneal infiltrates disappeared slowly from the recipient cornea, and the donor cornea remained free of infiltrates. On day 13 after transplantation, fluid from the anterior chamber was obtained for determination of the level of voriconazole. In addition, the voriconazole level in serum was determined. The voriconazole level in the aqueous humor, measured by an agar diffusion bioassay [3], was 3.2 µg/mL, which was 160% of the level in plasma (2 µg/mL), suggesting that topically applied voriconazole increased drug levels in the anterior chamber. The recent performance of penetrating keratoplasty may have created a situation that favored the absorption of the topically applied voriconazole. Cultures of corneal scrapings that had been obtained after 6 days of voriconazole treatment remained sterile.

After day 14 of treatment with intravenous and topical voriconazole, the treatment was changed to voriconazole tablets.
Figure 1. Histological images of the resected cornea. Rectangles in the overview (top) represent the areas that are enlarged in the lower panels. Arrows, examples of Fusarium solani hyphae. Note the extensive presence of fungi in both central areas (panels b and c) and peripheral areas (panels a and d) and in both superficial layers (panels a and b) and deep layers (panels c and d) of the cornea. The highest number of hyphae was found in the floor of the central ulcer (b). In the periphery of the cornea, the Bowman’s membrane was partly intact, but the epithelial lining was lacking (a), and, in other areas, hyphae were found next to Descemet’s membrane (d). However, hyphae were not found in the surgical margins of the cornea. (Overview [top], periodic acid-Schiff stain, original magnification ×10; panels a–d, periodic acid-Schiff stain, original magnification ×400).

(200 mg b.i.d.) and topically applied 1% voriconazole eyedrops administered 8 times a day. This regimen was continued to complete a 1-month course. This treatment regimen was well tolerated, with no apparent adverse effects. During the next 4 months, the cornea showed 1 rejection episode, which was well suppressed with locally applied steroids. However, because of slow endothelial decompensation, the cornea did not remain clear.

Discussion. Fusarium species are fast-growing hyalohyphomycetes, and identification through the use of cultures is usually possible within 4 days. These fungi are ubiquitous organisms that are present in soil, water, and plants, and they have been reported to be the most frequent cause of fungal keratitis, causing up to 32% of these infections [4]. Among the Fusarium species, F. solani is the most reported cause of infection [5]. Most infections have been reported in farmers, and the infections are often preceded by trauma. Other risk factors include the use of antibiotics and corticosteroids, preexisting eye diseases, surgery (e.g., laser-assisted in situ keratomileusis to treat refractive disorders), and the use of contact lenses. In the patient we describe, the source of infection may have been the body of water in which he had been swimming. His daily-wear, disposable contact lenses may have predisposed him to this infection.

Second-generation triazoles such as voriconazole and posaconazole appear to be promising for the treatment of fungal infections of the eye. Posaconazole was shown to penetrate the vitreous humor as well as the aqueous humor in a patient with a F. solani keratitis and endophthalmitis [6]. A prospective, nonrandomized clinical study involving 14 patients who were undergoing elective eye surgery for conditions other than fungal disease showed that, for most known cases of keratitis, oral administration of two 400-mg doses of voriconazole before surgery resulted in therapeutic concentrations in the plasma (in 14 patients; mean value ± SD, 2.13 ± 0.93 μg/mL), vitreous humor (in 14 patients; mean value ± SD, 0.81 ± 0.3 μg/mL), and aqueous humor (in 11 patients; mean value ± SD, 1.13 ± 0.57 μg/mL) [7]. The mean concentration in the aqueous humor (1.13 ± 0.57 μg/mL) was 53% of that in plasma (2.13 ± 0.93 μg/mL). It was suggested that the lack of inflam-
information of the patients’ eyes in that study may have resulted in lower drug concentration levels in the aqueous humor. Although voriconazole is effective in the treatment of *Fusarium* infections [8], the MICs of voriconazole are usually 4 μg/mL or >8 μg/mL [9]. This suggests that voriconazole may be ineffective to treat *Fusarium* infections unless high concentrations of drug reach the infected tissue. In fact, clinical failure in a patient with *Fusarium* keratitis treated with only oral voriconazole has been described [10]. We have previously shown that the voriconazole level in the aqueous humor was ~50% of the plasma level in a patient with fungal keratitis who was treated with only oral voriconazole for 12 days, a regimen that might be insufficient to treat a *Fusarium* keratitis [11]. One other case report suggested a beneficial effect of adding topical voriconazole to systemic treatment in *Fusarium* keratitis, although actual drug levels have not been measured [12].

In the patient we describe, the combination of systemic and topical voriconazole resulted in high drug levels in the anterior chamber without any apparent adverse effects. Although surgical intervention remains the cornerstone of treatment for severe fungal keratitis, systemic and topical voriconazole achieves higher drug levels, which may have contributed to the successful outcome in the patient we describe.

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**References**