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Successful Treatment of *Paecilomyces Lilacinus* Keratitis with Oral Posaconazole

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Abstract

Purpose—To report a case of successful medical treatment with oral posaconazole in refractory fungal keratitis caused by *Paecilomyces lilacinus*.

Methods—Case report.

Results—A 57-year-old male soft contact lens wearer presented with irritation, pain, photophobia and reduced vision. Slit-lamp examination showed a large corneal epithelial defect with a peripheral infiltrate. The patient did not improve on fortified topical antibiotics. Following diagnosis of *Paecilomyces lilacinus* fungal keratitis, oral voriconazole and topical antifungal therapy were started. Despite antifungal therapy, progressive disease required therapeutic penetrating keratoplasty (PKP). Postoperatively, due to clinical signs of recurrence and *in vivo* confocal microscopy (IVCM) findings of presumed hyphae in the cornea, intracameral miconazole was injected and oral posaconazole was started. The patient improved and demonstrated no hyphae 6 weeks after starting posaconazole. When posaconazole was stopped the cornea remained clear with excellent acuity. However, due to acute graft rejection 2 months after stopping posaconazole, keratoprosthesis was implanted, with no evidence of infection at surgery or during 3.5 years follow-up.

Conclusion—To our knowledge, this is the first report on the use of oral posaconazole for *Paecilomyces* keratitis. Posaconazole might be indicated in the treatment of refractory *Paecilomyces* keratitis resistant to conventional therapy.

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The authors state that they have no financial or conflicts of interests to disclose.

Keywords

Paecilomyces lilacinus; fungal keratitis; posaconazole; in vivo confocal microscopy

The ubiquitous saprophytic filamentous fungus *Paecilomyces lilacinus* is a rare cause of fungal keratitis and endophthalmitis and occurs more commonly in patients with predisposing factors such as contact lens wear.¹ *Paecilomyces* keratitis can be devastating due to its poor response to conventional antifungal therapy, often requiring therapeutic penetrating keratoplasty (PKP).¹⁻⁴ Herein, we describe successful treatment of refractory keratitis caused by *Paecilomyces lilacinus* with the use of oral posaconazole, a relatively new, generally well-tolerated, and highly potent triazole.

CASE REPORT

A 57-year-old male presented with irritation, pain, photophobia, and reduced vision in the right eye. He had worn soft contact lenses for 5 years, but practiced poor lens hygiene. At presentation, his uncorrected visual acuity was 20/100 in the right eye and 20/15 corrected in the left eye. Slit-lamp examination demonstrated a 5.8 × 6.3 mm central corneal epithelial defect, a peripheral 1.5 × 2.0 mm infiltrate at 1-o'clock position adjacent to the limbus, and stromal edema. After obtaining corneal cultures, fortified vancomycin and tobramycin were started, with bacitracin-polymyxin ointment at night. The infiltrate worsened. Nine days after initial presentation, cultures showed fungal growth. *In vivo* confocal microscopy (IVCM, Heidelberg Retina Tomograph 3/Rostock Cornea Module, Heidelberg Engineering, Heidelberg, Germany) showed presumed hyphae at 500 microns depth, supporting the diagnosis of fungal keratitis (Fig. 1 A). B-scan showed no endophthalmitis. Oral voriconazole 200 mg twice daily, as well as hourly topical amphotericin and natamycin were started; topical vancomycin plus tobramycin were stopped. Nineteen days after initial presentation, the fungus was identified as *Paecilomyces lilacinus* and topical voriconazole 1% was added. However, the epithelial defect and infiltrate (2.5 × 2.5mm) further worsened (Fig. 2 A and B), and visual acuity decreased to counting fingers.

By 22 days after presentation, a hypopyon developed and the patient underwent therapeutic PKP. Intracameral and subconjunctival injections of voriconazole (50 µg/0.1 ml) were given. Fungal stains and cultures of the aqueous and the removed cornea were negative, but histopathology demonstrated deep fungal elements in the corneal stroma (Fig. 3). Postoperatively, topical cyclosporine 2%, voriconazole 1%, and amphotericin B, all four times daily, were prescribed and oral voriconazole was continued. Despite continuation of antifungal therapy, increased anterior chamber inflammation, keratic precipitates, and a hypopyon were noted at 11 days postoperatively, with no obvious stromal infiltration. The presence of filamentous structures in the posterior stroma resembling those seen prior to PKP by IVCM (Fig. 1 B), together with the treatment response, and improvement in inflammation was highly suggestive for recurrence. An intracameral injection of miconazole (25 µg/0.1 ml) was given, and topical miconazole was started. The infectious disease unit was consulted the same day, and the patient was placed on oral posaconazole 400 mg twice daily. After 1 week of oral posaconazole treatment, he reported significant improvement in symptoms with an increase in uncorrected visual acuity from counting fingers at 2 feet to

20/200 and resolving inflammation. A second intracameral injection of miconazole was given. Antifungal susceptibility testing on the initial isolate, performed by a reference lab, returned showing high minimum inhibitory concentrations (MIC) for natamycin (>32 micrograms/ml at 48 hours), suggesting resistance. Susceptibility results for amphotericin were 2 micrograms/ml at 24 hours but >16 micrograms/ml, at 48 hours, while MIC's for voriconazole (0.25 at 24 hrs, 0.5 at 48 hrs) and miconazole (4 at 24 and 48 hrs) appeared favorable. Topical amphotericin was rapidly tapered off; topical miconazole and voriconazole were continued for 3 more months. Six weeks after starting posaconazole, IVCN revealed no evidence of inflammation or fungal elements (Fig. 1 C). During 5 months of posaconazole treatment the cornea remained clear centrally (Fig. 2 C and D), and the patient achieved a best-corrected visual acuity of 20/20 after cessation of antifungal therapy. Unfortunately, The patient developed acute graft rejection two months later and required a keratoprosthesis type I. There was no evidence of infection at surgery, and 3.5 years after keratoprosthesis placement, the patient remains free of infection and with vision 20/60.

DISCUSSION

To our knowledge, this is the first case report describing successful treatment of *Paecilomyces lilacinus* keratitis with oral posaconazole. This patient, who was refractory to other topical, oral and intracameral antifungal medications and presented with recurrent fungal keratitis after therapeutic corneal transplantation, showed significant improvement of symptoms and signs by 1 week after treatment with posaconazole and intracameral miconazole, with no evidence of fungal elements in IVCN after 6 weeks of treatment. Furthermore, no recurrence developed during the 3.5 years of follow-up.

Risk factors for *Paecilomyces* keratitis include contact lens wear, as in our patient, as well as ocular trauma, ocular surgery, steroid therapy, and IOL implantation.^{1,5-7} Clinically, although *Paecilomyces* keratitis has previously been described to characteristically involve the posterior stroma with an intact epithelium,^{2,4,8} our patient had a large epithelial defect. Since the clinical features are not pathognomonic for a fungal keratitis, cultures are required to detect specific species.

Particularly in cases where cultures are still pending or are inconclusive, IVCN has recently been described as an adjunct tool to locate fungal elements and has the potential to visualize them in the deep stroma.⁹ Although our patient received close follow-up with serial IVCN, filamentous structures were observed until 43 days after posaconazole was started, despite clinically significant improvement.

Successful medical treatment of *Paecilomyces* keratitis with other antifungal agents such as voriconazole has been reported.^{1,5-7} However, there was no improvement in our patient with voriconazole, suggesting that refractory cases exist and that alternative therapies, such as posaconazole, should be considered.

Posaconazole is a triazole antifungal and is usually well tolerated.⁸ Its efficacy on *Paecilomyces lilacinus* has recently been shown in a murine infection model.¹⁰ In addition, it has recently been used in a case with refractory keratitis due to *Beauveria bassiana*, as

reported by Tu et al.¹¹ Further, Sponzel et al. successfully treated a case of *Fusarium* keratitis, where posaconazole was used both orally and topically.¹² However, the commercial preparation of posaconazole available now is an oral suspension and should not be used topically as it contains various additives, including dyes.

Although our patient did not report any adverse effects during posaconazole therapy, the most common adverse effects are gastrointestinal symptoms, such as nausea and vomiting, as well as fever and headaches.⁸ In addition, liver function tests should be monitored regularly. Tu et al. reported that posaconazole had to be discontinued after one month of therapy due to the development of elevated liver function tests and pleural effusion.¹¹

A limitation of this case report is the concurrent treatment with intracameral and topical miconazole. Antifungal susceptibility testing showed low MIC's for both voriconazole and miconazole. Nevertheless, there was no improvement on initial voriconazole therapy, even though its MIC was lower than for miconazole. In addition, topical drops alone are unlikely to be effective in deep stromal lesions. Moreover, after intracameral miconazole filamentous hyphae were still observed by IVCN and thus it is very unlikely that miconazole resulted in eradication of the fungus. Nevertheless, an additional therapeutic effect of miconazole or any of the other antifungal drugs cannot be completely excluded.

In summary, this case report indicates that oral posaconazole may serve as an effective treatment for refractory *Paecilomyces* keratitis, resistant to conventional therapy.

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Figure 1.

In vivo confocal microscopy in *Paecilomyces lilacinus* keratitis. Preoperative IVCM of the right eye shows filamentous structures in the deep posterior corneal stroma at around 500 microns depth (long arrows) (A). Postoperative IVCM shows filaments (short arrows) resembling those seen prior to PKP (B), which resolved after 43 days of posaconazole treatment (C).

Figure 2.

Pre- and postoperative slit lamp exams in *Paecilomyces lilacinus* keratitis. The right eye demonstrates an infiltrate at 1 o'clock position adjacent to the limbus (**A**). Corneal fluorescein staining shows a large overlying epithelial defect (**B**). Superior scarring after recurrent keratitis, and a clear visual axis (**C**). Neovascularization and superior scarring due to partial limbal stem cell deficiency (**D**).

Figure 3. Histopathology of the cornea (Gomori-Grocott methenamine silver (GMS) stain). The greatest density of fungal elements can be seen in the posterior corneal stroma (inferior in image).