Successful Treatment of Chronic Stromal *Acanthamoeba* Keratitis With Oral Voriconazole Monotherapy

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Purpose: To describe the treatment of chronic stromal *Acanthamoeba* keratitis (AK) with oral voriconazole monotherapy.

Methods: All cases of chronic stromal AK recalcitrant to traditional therapy subsequently treated with systemic voriconazole seen at the University of Illinois Eye and Ear Infirmary between June 2003 and July 2009 were reviewed for clinical presentation, clinical course, and outcome.

Results: Three eyes of 2 patients were identified with culture-confirmed chronic stromal AK unresponsive to traditional anti-acanthamoebal therapies, requiring topical corticosteroids to maintain corneal clarity. Oral voriconazole 200 mg twice daily achieved a rapid but transient reduction of inflammation and elimination of corticosteroid dependency but, in both patients, recrudesced approximately 6 weeks after its discontinuation. Subsequent repeated and/or extended use of oral voriconazole alone resulted in complete resolution ranging from 7 to 11 months off all medications with final best-corrected visual acuity ranging from 20/20 to 20/25.

Conclusions: Recalcitrant chronic *Acanthamoeba* stromal keratitis was successfully treated with extended systemic voriconazole administration with good preservation of vision. The clinical resolution of chronic stromal keratitis in our 2 cases suggests that voriconazole may have a larger role in the treatment of AK.

Key Words: *Acanthamoeba*, voriconazole, keratitis, stromal interstitial keratitis

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The prognosis for patients with *Acanthamoeba* keratitis (AK) has improved significantly over the past 2 decades with the introduction of topical biguanides, but medical options remain limited for cases failing to respond to current medical therapy, especially those with deeper corneal involvement sometimes requiring surgical intervention.[1] One potential class of drugs, the azoles that act to interrupt the synthesis of ergosterol, an integral component of fungal cell walls that has also been identified in the plasma membrane of *Acanthamoeba sp.* have been suggested in the treatment of AK.[2] The successful use of earlier generation azoles, such as miconazole, clotrimazole, and itraconazole, for AK has been reported previously.[3–6] Unfortunately, these cases almost always involved their adjunctive use with other established antiacanthamoebal drugs or, rarely, surgery, thereby making it difficult to determine the actual contribution of each individual agent.

Newer triazoles, specifically voriconazole (Vfend; Roerig/Pfizer, Inc, New York, NY), have been shown to have significantly improved in vitro activity and tissue penetration for fungi but with the additional presumptive evidence of efficacy in systemic *Acanthamoeba* infection.[2,7] However, success in systemic disease is preliminary and not universal.[8] We report 2 cases of steroid-dependent stromal AK refractory to traditional therapy treated with oral voriconazole monotherapy.

CASE REPORTS

Case 1

A 17-year-old girl was referred to the University of Illinois Eye and Ear Infirmary (IEEI) with a 1-month history of bilateral contact lens–related keratitis complaining of blurred vision and ocular discomfort. She reported using AMO Complete MoisturePlus and having poor lens hygiene habits. Prior treatment with topical gatifloxacin and ciprofloxacin ointments was unsuccessful, experiencing symptomatic improvement only after topical corticosteroids were started 2 weeks before. Visual acuity was 20/40 and 20/30 in the right and left eyes, respectively. She exhibited a bilateral epitheliitis with relative peripheral corneal clearing accompanied by a radial keratoneuritis in the left eye. Confocal microscopy and a smear, using the Diff-Quik (Difco, Detroit, MI) modified Romanowsky stain, both demonstrated *Acanthamoeba* cysts with positive cultures reported the next day. The patient was treated with topical propamidine isethionate (Brolene; Sanofi-Aventis, Paris, France) and chlorhexidine gluconate 0.02%, tapered over the next 5 months by her private ophthalmologist. Her vision returned to 20/20 OU when she independently elected to return to contact lens wear.

She again presented to her ophthalmologist complaining of blurred vision and photophobia 6 months later and was treated with low-dose corticosteroids for bilateral stromal keratitis. After 5 months of therapy, she was referred to the IEEI for a persistently symptomatic and slowly progressive steroid-dependent multifocal stromal keratitis without epithelial and endothelial involvement or neovascularization. Confocal microscopy was positive for *Acanthamoeba* in the left eye (Fig. 1) and equivocal in the right eye. Scrapings were not performed at this visit because her anterior cornea seemed uninvolved.

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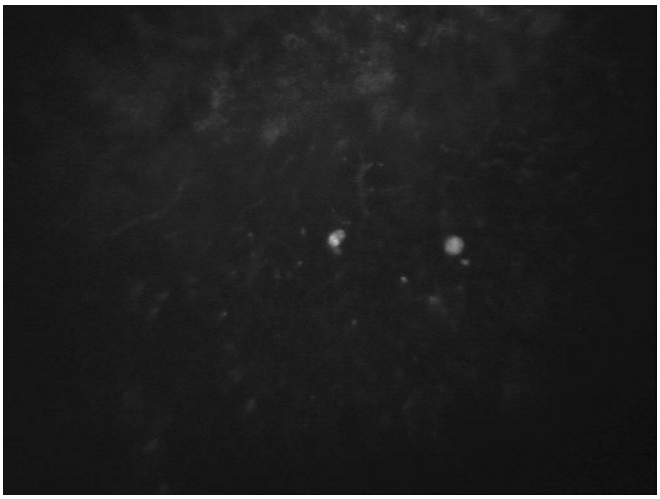

FIGURE 1. Confocal microscopy showing a dense, circular, bright white opacity characteristic of the cyst form of *Acanthamoeba* after 5 months of steroid therapy for inflammatory stromal keratitis (case 1).

Propamidine and polyhexamethylene biguanide 0.02% were prescribed hourly with the addition of voriconazole 200 mg twice daily by mouth because of the deep keratitis. Propamidine was discontinued after 1 day because of intolerance; despite this, the patient was able to eliminate steroid use over the next 3 weeks. Polyhexamethylene biguanide was continued for a total of 4 months, tapered to 4 times daily after 6 weeks. The voriconazole was discontinued at the same time. Inflammation returned 6 weeks later, and voriconazole 200 mg twice daily without corticosteroids was again introduced for 2 additional months with good subjective and objective responses. Eleven months later, she remained asymptomatic with a complete resolution of her corneal inflammation. Liver function tests were monitored throughout her course of therapy and remained normal. Final spectacle-corrected visual acuity was 20/25 and 20/20 in the right and left eyes, respectively.

Case 2

A 14-year-old boy presented on July 2006 to the IEEI with an 8-month history of stromal keratitis of the left eye with significant redness, blurred vision, and photophobia. He initially had symptoms in November of 2005 after swimming while wearing his contact lenses while vacationing in St Lucia. The patient had failed treatment with commercially available topical antibacterials and antivirals and was now reliant on topical corticosteroids for comfort. Visual acuity was 20/30, best corrected in the affected eye. Deep and superficial stromal inflammatory lesions found both in the peripheral and central cornea were occasionally associated with deep neovascularization extending from the limbus. Minimal epithelial or endothelial changes were noted, and no ring-type infiltrate was present. Confocal microscopy was equivocal likely because of the density and depth of the infiltrates. Cultures were initially negative. Immune and infectious serologic tests including syphilis, herpes simplex virus, Epstein–Barr virus, and Lyme disease were also negative. Stromal lesions slowly progressed, and the patient remained symptomatic despite empiric chlorhexidine 0.02% for 10 weeks and courses of systemic itraconazole and valacyclovir. (Fig. 2) A corneal biopsy was then performed and showed chronic nongranulomatous inflammation and no organisms. The patient remained dependent on a minimum of

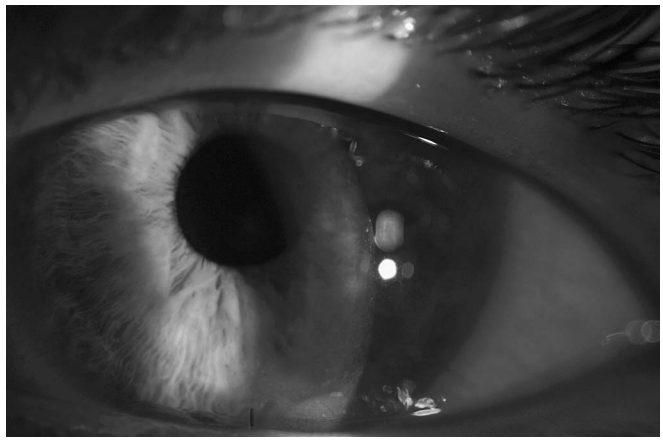

FIGURE 2. Slit-lamp photograph demonstrating central stromal keratitis and inferior corneal vascularization related to *Acanthamoeba* (case 2).

1–2 times per week topical corticosteroids and Restasis (Allergan, Irvine, CA) twice a day with occasional but significant exacerbations.

Six months after initial presentation, the original specimen was reprocessed using methods appropriate for naked amoeba, which now yielded a positive culture for *Acanthamoeba*. After extensive discussion and informed consent, the patient was given a course of oral voriconazole 200 mg twice daily for 2 months without concomitant topical treatment. The patient was able to discontinue low-dose topical steroids 6 weeks later. Six weeks after discontinuing voriconazole, mild recurrent inflammation ensued. Further antiacanthamoebal therapy was offered, but the family elected to continue use of periodic topical corticosteroids only. Episodes continued for the following 14 months until a severe episode of stromal keratitis occurred in October 2008. A 6-month course of oral voriconazole was administered with rapid and sustained resolution of corneal inflammation without the need for corticosteroids. The eye remained completely free of inflammation 7 months after discontinuing the drug. Liver function tests were monitored throughout his course of therapy and remained normal. Final best-corrected visual acuity was 20/25.

DISCUSSION

Our 2 cases represent patients with culture-confirmed chronic *Acanthamoeba* stromal keratitis resistant to treatment with traditional antiacanthamoebal medications successfully treated with oral voriconazole monotherapy. Although voriconazole was initially used in conjunction with other antiacanthamoebal drugs, recurrent inflammation resolved with the sole, extended, or repeated use of systemic voriconazole. Each introduction of voriconazole induced a rapid reduction in inflammation and allowed for a discontinuation of chronic topical immunosuppressant use with a stable improvement of both vision and comfort.

Voriconazole exhibits better oral absorption and tissue penetration characteristics and significantly greater efficacy in fungal infections than previous generation azoles. We chose to use the drug systemically in these patients because of their deeper corneal involvement and to obtain more consistent drug levels. Also, because the sole use of traditional topical antiacanthamoebal drugs did not result in a similar response,

we elected to treat with systemic medications alone for subsequent courses to avoid any barrier effects of the intact epithelium present in our patients. Topical voriconazole 1% has been suggested to have good corneal penetration in the setting of active inflammation and may, in the future, be evaluated as an alternative mode of delivery in patients with active epithelial disease.[9]

Although primarily an antifungal agent, successful use of voriconazole has been previously reported in disseminated systemic *Acanthamoeba* infection but only as part of a 3-drug post–penetrating keratoplasty regimen for AK.[7,10] In vitro studies have shown good activity against *Acanthamoeba* trophozoites and rapid suppression of *Acanthamoeba* cysts.[2] It is important to note that, in vitro, although exposure to the drug results in rapid suppression, extended exposure to the drug is required for cidal activity.[2] Correspondingly, either extended or multiple courses of voriconazole were required in our patients before sustained resolution of inflammation was achieved. Recurrences, if they were to occur, presented within 6 weeks of discontinuing therapy in the form of recrudescent inflammation.

Although a small proportion of chronic *Acanthamoeba* stromal keratitis may be immune rather than infectious,[11] the resolution of inflammation in our patients with antibiotic treatment strongly suggests continued infection. It is unknown whether the subsequent infection in case 1 represents reactivation or a new infection because the disease may remain dormant for over a year.[12] Regardless, confocal microscopy was positive, and the patient experienced a rapid treatment response. In case 2, the patient required periodic topical corticosteroids to suppress corneal inflammation almost continuously from the time of initial presentation but was only able to discontinue these permanently after oral voriconazole, further suggesting persistent infection.

Although ideally voriconazole would have been the only drug used during the course of therapy, the clinical response in our refractory culture-confirmed cases presents the clearest indication to date of the efficacy of oral voriconazole as a single agent for the medical treatment of chronic stromal AK. Despite the availability of highly efficacious topical anti-acanthamoebal therapy, there remains a subset of patients who respond poorly and require alternative effective compounds or surgical intervention.[13,14] Although a number of compounds have been reported as additive or adjunctive drugs for AK therapy, only a few have been demonstrated to be independently efficacious as monotherapeutic agents.[15] Voriconazole should, therefore, be considered in the treatment of chronic stromal keratitis related to *Acanthamoeba* infection and further studied for use in other forms of AK.

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