Successful Topical Application of Caspofungin in the Treatment of Fungal Keratitis Refractory to Voriconazole

Fungal keratitis is an important ophthalmic problem because it leads to corneal blindness and sometimes to loss of the eye.1,2 There is no agreed protocol for the treatment of suspected fungal keratitis. Topical and oral voriconazole have now been reported to be effective.3 However, some cases do not respond to this treatment. New antifungal agents such as caspofungin acetate, 0.5%, are promising alternatives.

Report of a Case. A 60-year-old woman with a history of penetrating keratoplasty in her right eye due to corneal herpetic infection 1 year earlier was admitted because of visual disturbances and ocular pain. Slitlamp examination revealed an epithelial defect with corneal infiltration (Figure, A). Corneal scrapings were taken for smear and culture, and Candida albicans was isolated. We asked our pharmacology service for amphotericin B eyedrops but were informed of solubility and stability problems with the actual presentation of this drug. Treatment with topical voriconazole, 1%, administered every hour and oral voriconazole at a dosage of 200 mg twice daily was started. After 1 month the lesion had not progressed but there was no change in corneal infiltration, and cultures remained repeatedly positive for C albicans with no evidence of viral infection (Figure, B). Therefore, after obtaining the patient’s consent and permission of sanitary authorities, we decided to apply topical caspofungin, 0.5%, every hour. To obtain the eye-drops, 1 vial of 50 mg of caspofungin acetate was diluted in 10.5 mL of sterile normal saline; all eyedrops were freshly made daily, kept at 4°C, and protected from light. One week later, clinical improvement was observed and cultures revealed no growth (Figure, C). Treatment with

Figure. Evolution of the case. A, Epithelial defect with corneal infiltration. Corneal scrapings were taken for smear and culture, and Candida albicans was isolated. B, One month after starting treatment with topical voriconazole, cultures remained positive for C albicans. C, One week after starting treatment with topical caspofungin acetate, clinical improvement was observed and cultures revealed no growth. D, Four weeks after starting treatment with topical caspofungin, complete healing of the corneal epithelium and resolution of the corneal infiltrate were observed. However, the corneal opacity persisted (a neglected suture was removed).
topical caspofungin was progressively decreased over 3 further weeks. Following the completion of treatment, complete healing of the corneal epithelium and resolution of the corneal infiltrate were observed, although the corneal opacity persisted (Figure, D). There was no evidence of ocular toxic effects and no recurrence of fungal keratitis over a follow-up period of 6 months.

Comment. *C. albicans* is the most frequent cause of fungal keratitis in temperate regions and is an opportunistic organism that can complicate chronic keratopathy and corneal grafting. Persistent epithelial defects and suture-related problems, along with immunosuppression, have been found to be the major predisposing risk factors.

Caspofungin is a first-in-class echinocandin with potent activity against *Candida* and *Aspergillus*, the dominant human fungal pathogens. In contrast to all other antifungal drugs, echinocandins have a selective action on a target present only in fungal cell walls (not in mammalian cells), they inhibit the synthesis of an essential component, (1,3)-β-glucan. Caspofungin is fungicidal in vivo and in vitro against all *Candida* species, including fluconazole-resistant strains. Its activity differs from that of the azole antifungal group, which is fungistatic. In our case, we think that voriconazole stopped progression of the infiltrate but did not kill the microorganism. The presence of the fungus after 1 month could be due to poor drug penetration, fungal resistance, or both. We therefore suggest that an ideal treatment protocol should include antifungal agents chosen on the basis of in vitro susceptibility of the fungus with a duration assessed by drug penetration, fungal resistance, or both. We therefore suggest that an ideal treatment protocol should include antifungal agents chosen on the basis of in vitro susceptibility of the fungus with a duration assessed by drug penetration, fungal resistance, or both.

To our knowledge, the topical ocular use of caspofungin has been reported in rabbits. There has been only 1 report of its use in humans, although it was in association with other antifungal drugs.

In conclusion, topical caspofungin, 0.5%, is a new, promising option in the treatment of refractory fungal-related corneal ulcers with no evidence of ocular toxic effects. However, future studies with larger samples are indicated to further evaluate its efficacy and tolerance.

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