

Intrastromal voriconazole: the next effective adjunctive treatment for recalcitrant keratomycosis

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Abstract

Introduction: Fungal keratitis is a commonly encountered infection of the cornea which may lead to moderate to severe visual loss.

Aim: To report the result of intra-stromal voriconazole in refractory keratomycosis.

Method: Fungal keratitis is a commonly encountered infection of the cornea which may lead to moderate to severe visual loss. It may be caused by several species of fungi and accounts for nearly 50% of all cases of infectious keratitis in developing countries. The penetration of antifungal drugs into the deeper layers of cornea is sub-optimal, thus making it difficult to treat cases of deep fungal keratitis. We report two cases of refractory fungal keratitis; one caused by aspergillus fumigates and other by fusarium as seen on lactophenol cotton blue mount from scrapings. Both the cases were resistant to topical 5% natamycin and 1 % voriconazole and therefore, intra-stromal voriconazole reconstituted to 50 microns / 0.1 ml was injected circumferentially into the mid-stroma in close proximity to the ulcer margins in both the cases.

Result: A marked reduction in the size of ulcer (both epithelial defect and infiltrates) was noted at 72 hours after intra-stromal voriconazole. A repeat injection was given in both the cases four days after the first injection. No complications were seen in any of the cases.

Conclusion: Intra-stromal voriconazole offers an effective adjunctive in treating refractory keratomycosis as the direct deposition of drug into deeper stroma results into higher therapeutic concentrations into ulcer; thus obviating the need for therapeutic penetrating keratoplasty in such patients.

Keywords: Keratomycosis; Recalcitrant ulcer; Anti-fungal agents; Intra-stromal injection; Voriconazole

1. Introduction

Fungal keratitis is a commonly encountered infection of the cornea which may lead to moderate to severe visual loss. It may be caused by several species of fungi and accounts for nearly 50% of all cases of infectious keratitis in developing countries [1, 2]. The available antifungal drugs for the treatment of fungal keratitis are less effective than the antibacterial drugs for bacterial keratitis. Moreover, the penetration of antifungal drugs into the deeper layers of cornea is sub-optimal, thus making it difficult to treat cases of deep fungal keratitis. To overcome these issues, various investigators have evaluated alternate routes such as intracameral and intrastromal injections of amphotericin B and voriconazole to treat fungal keratitis. We report two cases of fungal keratitis which were refractory to topical medications, but responded very well to intra-stromal and intra-cameral voriconazole injections.

2. Method

We selected two patients with severe fungal keratitis which were diagnosed on the basis of clinical findings and microbiological examination. Both patients underwent detailed slit lamp examination. Corneal scrapings were taken for potassium hydroxide (KOH) mount, lactophenol cotton blue mount (LCB), gram staining; and culture on the blood agar, chocolate agar and Sabouraud Dextrose Agar (SDA) medium which were positive for fungus.

2.1. Case 1

A 14 year old male presented with complaints of redness, watering, photophobia, pain and progressive diminution of vision in right eye (R/E) for the last 1 month following a finger nail trauma. The patient was instilling topical natamycin 5% and voriconazole 1% and had received an intra-cameral with intrastromal amphotericin B from outside 1 week before presenting to us. On examination,

Visual acuity was 20/200 in R/E and 20/20 in left eye (L/E). On slit lamp examination, R/E showed a dry looking full thickness eccentric corneal ulcer with epithelial defect 5.1x6.2mm and underlying infiltrates 5.4x 6.8mm with feathery margins. Cultures from scrapings were positive for

Aspergillus fumigates. (Figure 1) The patient was also started on oral itraconazole after doing baseline liver function tests. With no response to the current treatment for another week, a diagnosis of recalcitrant fungal keratitis was made and patient was considered for intrastromal voriconazole injection.

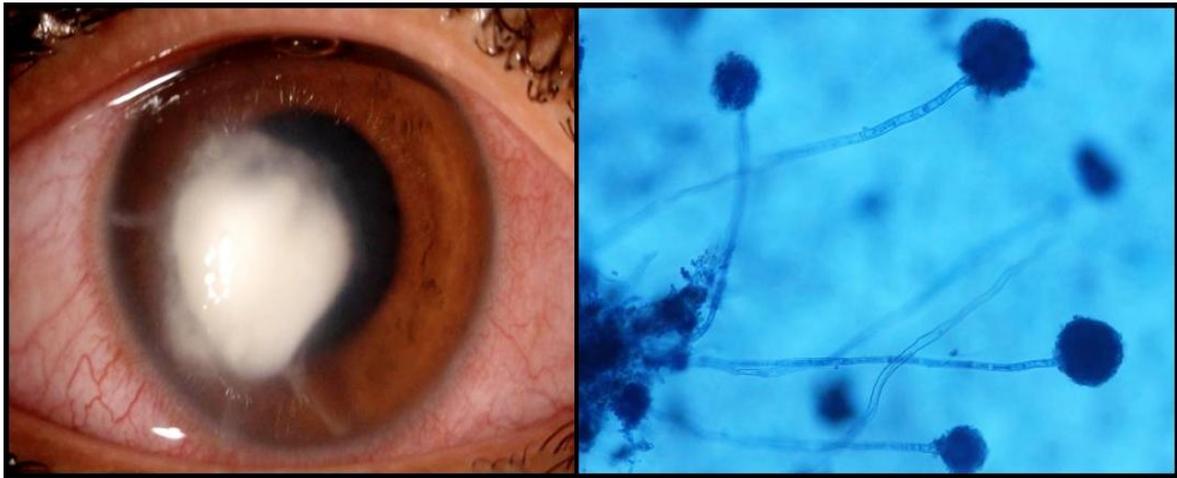


Figure 1: Slit lamp picture of right eye showing large fungal ulcer (left); lactophenol cotton blue (LCB) preparation from scrapings showing *Aspergillus fumigates* (right).

2.2. Case 2

A 35 year old male presented with similar complaints of pain, redness, watering, photophobia and whitish discoloration of R/E for 2 weeks. The symptoms, which kept progressing after onset, started after fall of some vegetative foreign body into the eye. On examination, visual acuity R/E was 20/400 and L/E was 20/20. On slit lamp, conjunctiva showed marked circumciliary flush. There was a large round epithelial defect of about 5.5mm diameter with underlying whitish infiltrates (5.8x6.7mm) involving full stromal thickness in the central cornea with feathery margins

and a convex hypopyon of 2.5mm maximum height. A provisional diagnosis of keratomycosis was made and corneal scrapings were sent for microbiological investigation, the results of which showed growths suggestive of fusarium species. (Figure 2) The patient was started on topical natamycin 5% and voriconazole 1% and oral itraconazole. After 2 weeks of topical and systemic antifungals, no significant improvement was noted. Intrastromal voriconazole was given keeping in view the resistance of ulcer to the given treatment.

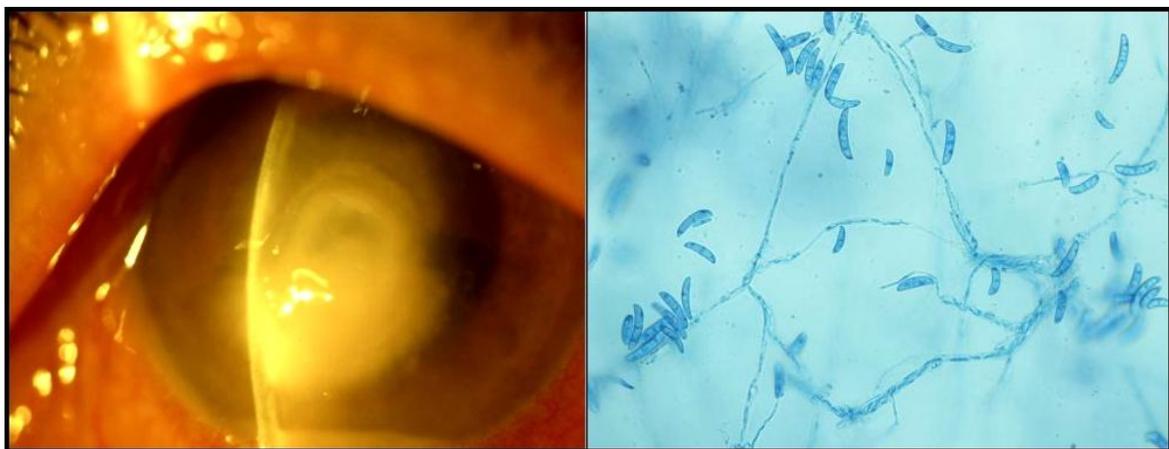


Figure 2: Slit lamp picture of right eye showing large central fungal ulcer with hypopyon (left); lactophenol cotton blue (LCB) preparation from scrapings showing fusarium species (right).

2.3. Technique

Injection voriconazole was reconstituted to 50 microns / 0.1 ml and was loaded in 1ml tuberculin syringe with 30G needle. Under topical anesthesia by proparacaine hydrochloride 0.5%; with needle bevel up, IJBR (2016) 7(05)

multiple intrastromal injections were given circumferentially into the mid-stroma in close proximity to the ulcer margin. A sufficient hydration of stroma was taken as end point of each injection. The patient was continued on topical and systemic antifungals following injection.

3. Result

A marked reduction in the size of ulcer (both epithelial defect and infiltrates) was noted at 72 hours after intra-stromal voriconazole. The hypopyon in first case reduced to 1mm after first injection. A second injection was

given after 4 days in both the cases. After another 72 hours, the ulcer size further reduced in both the cases with complete resolution of hypopyon in second case (Figure 3). The patients were symptomatically better. The topical and oral antifungals were continued.

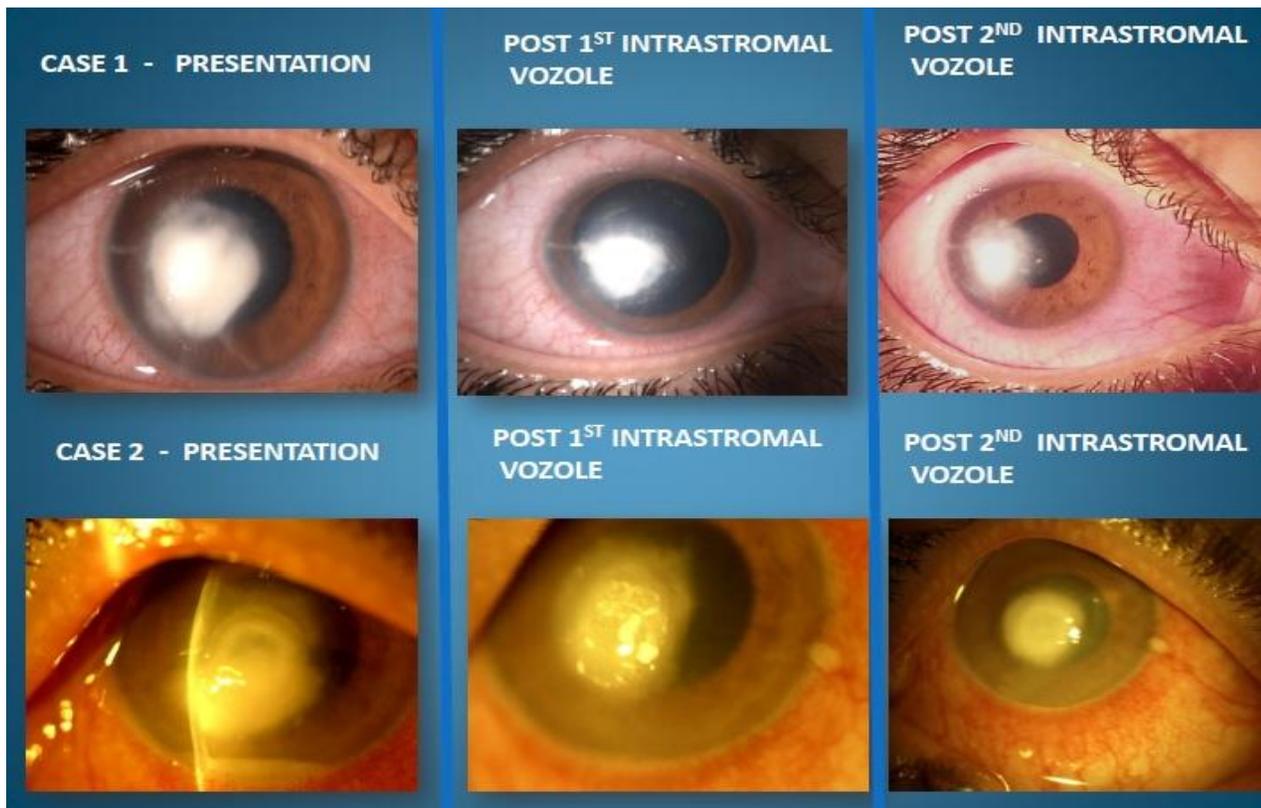


Figure 3: Serial slit lamp pictures of case 1 (upper row) and case 2 (lower row) showing response to two intrastromal voriconazole injections from left to right.

4. Discussion

Fungal keratitis is a common corneal infection particularly seen in developing countries usually in patients having history of trauma with vegetative matter. One of our cases had finger nail trauma and other had history of fall of some vegetative foreign body into his eye. Both the cases were resistant to topical anti-fungal medication but responded well to voriconazole when injected intrastromally in close proximity to the ulcer. We used voriconazole because previous experiences with it in ocular infections, using both topical and systemic routes, have been promising as per literature [3]. Furthermore, voriconazole has optimal activity against fungi that are resistant to amphotericin B and itraconazole and has a good safety profile as per reports [4, 5]. One of our cases had also received a dose of intrastromal with intracameral amphotericin B before presenting to us, with no response to the drug. The patient, however showed a striking response when intrastromal voriconazole was administered. The drug belongs to triazole group which inhibits synthesis of ergosterol, an essential component of the fungal cell wall. Voriconazole is ideal for use in fungal keratitis, as it has a broad spectrum against fungi with low

minimum inhibitory concentrations (MIC), as well as a high systemic intraocular penetration profile [6]. The drug is potent against many species of fungi, namely, the most common pathogens *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Aspergillus fumigatus*, *Aspergillus flavus*, *Fusarium solani* and other less common pathogens from the *Paecilomyces*, *Histoplasma*, *Scedosporium*, *Curvularia*, and *Acremonium* species [7]. Intra-stromal voriconazole might be a safe and effective method as reported by Kalaiselvi *et al* in 25 patients with culture proven fungal keratitis, not responding to a combination of topical 5% natamycin and 1% voriconazole. The drug helped to resolve infection in 18 (72%) patients and about 15% of these needed more than one injection. However, *Fusarium* keratitis cases showed suboptimal response in 6 out of 7 cases in their series [8]. Prakash G *et al* also reported positive response of intrastromal voriconazole in 2 cases of *Fusarium* species and one case of *Aspergillus* species [9]. In our study, one case with proven *Fusarium* species and another with *Aspergillus fumigatus* showed a notable response with intrastromal voriconazole. The intrastromal injections of voriconazole helped in early response of the ulcers with drastic clinical and symptomatic improvement in both the cases. Though this is a small study,

we believe that an astute use of intrastromal voriconazole as an adjunctive to topical drugs may be of great benefit in cases of resistant keratomycosis.

5. Conclusion

Intra-stromal voriconazole could be an effective alternative in treating refractory keratomycosis which are non-responding or poorly responding to topical anti-fungal therapy. The direct deposition of drug into deep stroma offers advantage over topical medications which are unable to penetrate and achieve therapeutic concentrations into deep stroma; thus obviating the need for therapeutic penetrating keratoplasty in such patients.

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