Evaluation of Intrastromal Injection of Voriconazole as a Therapeutic Adjunctive for the Management of Deep Recalcitrant Fungal Keratitis

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• PURPOSE: To evaluate the role of intrastromal injection of voriconazole in the management of deep recalcitrant fungal keratitis.
• DESIGN: Interventional case series.
• METHODS: SETTING: Cornea services at a tertiary care teaching hospital. PATIENTS: Three eyes of three patients with deep stromal recalcitrant fungal keratitis not responding to topical antifungal medications. INTERVENTION PROCEDURE: Voriconazole 50 micrograms/0.1 ml was injected circumferentially around the fungal abscess in the corneal stroma as an adjunctive to the topical antifungal therapy. MAIN OUTCOME MEASURE: Main outcome measure was a reduction in size of the abscess and resolution of the infection.
• RESULTS: Before the intracorneal injection, all three eyes had gradually worsening lesions on topical medications. After the intervention, a faster reduction in the size of corneal infiltration was documented and a complete resolution of the ulcers was seen within three weeks in all cases.
• CONCLUSION: Targeted delivery of voriconazole by intracorneal injection may be a safe and effective way to treat cases of deep-seated recalcitrant fungal keratitis responding poorly to conventional treatment modalities.

METHODS

IN THIS INTERVENTIONAL CASE SERIES, THREE CASES OF mycotic keratitis involving deep corneal stroma that were unresponsive to topical antifungal therapy underwent intrastromal injection of voriconazole 50 micrograms/0.1 ml. Each of the participating patients gave informed written consent for participation in the study and for the surgical and medical management.

The diagnosis of fungal infection was made on the basis of clinical evaluation, positive smear, and cultures of the fungus. At initial presentation, each patient underwent a detailed clinical evaluation that included recording of medical history, Snellen visual acuity testing, and slit-lamp biomicroscopy. Corneal scrapings were obtained under topical anesthesia and were sent for microbiological investigation including potassium hydroxide (KOH) wet-mount preparation, Gram smear, and cultures on blood agar, chocolate agar, and Sabaroud agar. Topical antifungal therapy was started as soon as fungus was identified by KOH wet-mount preparation, Gram smear, and cultures on blood agar, chocolate agar, and Sabaroud agar. Topical antifungal therapy was started as soon as fungus was identified by KOH wet-mount preparation and Gram smear. The initial topical therapy included drops of 5% natamycin every two hours, drops of 1% homatropine sulfate thrice a day, and topical 0.3% ciprofloxacin four times a day. If no objectively demonstrable response to therapy was seen in 14 days or if infection showed signs of worsening, patients were started on topical voriconazole 1% eye drops once each hour. If no response to this combined therapy was observed after two weeks, an antifungal drug was injected intrastromally around the fungal abscess. Each of the three cases had deep stromal abscess and no evidence of perforation (Figure).

• METHOD OF INTRASTROMAL INJECTION: Injection voriconazole (VFEND; Pfizer Inc, New York, New York, USA) is available as 200 mg of white lyophilized powder in a glass vial. The powder was reconstituted with 19 ml of lactated Ringer solution (LR) to obtain 20 ml of clear concentrate containing 10 mg/ml of voriconazole. A 1-ml

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aliquot of this solution was further diluted with 20 ml of LR to a concentration of 0.5 mg/ml (50 µg/0.1 ml). The reconstituted solution was loaded in a 1-ml tuberculin syringe with a 30-gauge needle.

After administration of peribulbar anesthesia, the patient was shifted to the operating table. Under full aseptic conditions, the preloaded drug was administered under operating microscope. With the bevel down, the needle was inserted obliquely from the uninvolved, clear area to reach just flush to the abscess at the mid-stromal level (as the intended level for drug deposit) in each case. The drug was injected and the amount of hydration of the cornea was used as a guide to assess the area covered. Once the desired amount of hydration was achieved, the plunger was withdrawn slightly to ensure discontinuation of the capillary column and thus prevent back-leakage of the drug. Five divided doses were given around the abscess to form a deposit of the drug around the circumference of the lesion. This was done in such a manner that a centripetally directed progressive wave of fluid appeared to encompass the abscess along each meridian.

Circumferential injection ensured the formation of a barrage of intrastromal voriconazole around the entire abscess. The total amount of drug injected intrastromally ranged from 0.05 ml to 0.10 ml. Intraoperative complications, if any, were recorded.

Postintrastromal injection, all patients were continued on prescribed topical antifungal therapy. Patients were examined every third day and response to the therapy was recorded, including best-corrected visual acuity (BCVA) and measurement of size of abscess on slit-lamp biomicroscopy. The infection was considered resolved when there was complete healing of epithelial defect with resolution of corneal abscess and scar formation. The patients were continued on topical antifungal therapy for at least one week after the complete resolution of infection.

RESULTS

EACH OF THE THREE PATIENTS WAS REFERRED TO US FOR MANAGEMENT BY THE PERIPHERAL OPHTHALMIC CLINICS WITH A HISTORY OF RECALCITRANT MICROBIAL KERATITIS AND HAD CORNEAL ABSCESSES INVOLVING UP TO POSTERIOR STROMA. PATIENTS HAD ALREADY RECEIVED TOPICAL FLUOROQUINOLONE DROPS AND ANTIMICROBIAL AGENTS FOR TWO TO FOUR WEEKS.
History of vegetative trauma was recorded in two patients, and one of these (Case 2) was treated with topical steroids (Table). In each of the three patients smears were positive for fungus and on cultures Fusarium species was identified in two eyes (Cases 1 and 3) and Aspergillus species in one eye (Case 2).

As poor response was seen following two weeks of therapy with topical eye drops of natamycin 5% and voriconazole 1%, voriconazole was injected intrastromally around the infected area. In each of the three patients the procedure was performed successfully and no intraoperative or postoperative complications were observed. In one patient (Case 2), there was minimal intrastromal bleeding in the inferior part of the cornea but this resolved in seven days. Systemic voriconazole 200 mg twice a day was additionally given to one patient (Case 3) because of scleral involvement. The infection resolved completely in all three eyes after the intrastromal injection of voriconazole (Figure). The mean healing duration was 18.6 ± 4 days (Table). Only a mild improvement in BCVA was seen in the three cases attributable to involvement of the abscess and the resultant scar in the central cornea.

**DISCUSSION**

*CORNEAL INFECTIONS INVOLVING DEEPER PARTS OF THE STROMA ARE NOT AMENABLE TO TOPICAL ANTIMICROBIAL THERAPY.*

This is particularly true for mycotic keratitis because none of the present-day antifungal agents can optimally penetrate the deeper layers of the cornea. To overcome these problems, modalities of targeted drug delivery are being evaluated. Similar attempts of site-directed drug deposit have been made in posterior segment pathologies in the form of intravitreal injections and posterior Sub-tenon injections of drugs.

In our small series, none of the three cases had responded to topical antifungal therapy and therefore we decided to proceed with intrastromal drug delivery. Intrastromal injections of amphotericin B have been used previously to treat recalcitrant mycotic keratitis. We used voriconazole because previous experiences with it in ocular infections, using both topical and systemic routes, have been promising. Furthermore, voriconazole has optimal activity against fungi that are resistant to amphotericin B and itraconazole and has a good safety profile. The intrastromal injections of voriconazole helped in early and complete resolution of the ulcers with no adverse effects.

Our small series of three cases provides some indication of a possible therapeutic role of intrastromal antimicrobial drug delivery by intrastromal injection in the management of recalcitrant fungal keratitis. We believe that if combined with topical therapy, a judicious use of intrastromal administration of antifungal drugs may be of immense benefit in such cases.

**REFERENCES**


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