International Journal of Biomedical Research
ISSN: 0976-9633 (Online); 2455-0566 (Print)
Journal DOI: https://doi.org/10.7439/ijbr
CODEN: IJBRFA

Original Research Article

Treatment outcomes of intrastromal Voriconazole injection for fungal keratitis

Trakanta Wannapanich* and Orapin Anutarapongpan

KKU Eye Center, Department of Ophthalmology, Faculty of Medicine, Srinagarind Hospital, Khon Kaen University, Thailand

Abstract

Objectives: To study the treatment outcomes of intrastromal voriconazole injections in patients with resistant mycotic keratitis in terms of clinical characteristics and associated risk factors for treatment success.
Methods: We retrospectively reviewed 70 medical records at a tertiary referral center in Northeastern Thailand from November 2015 to January 2020. The patients had fungal keratitis resistant to topical antifungal eye drops, with or without systemic antifungal therapy, and underwent intrastromal voriconazole injection. The recorded data included demographic information, possible risk factors, microbiological studies, clinical findings, procedures, clinical outcomes, and complications of the injections.
Results: Of the 70 patients, 15.2% showed improvement, while the others required therapeutic penetrating keratoplasty (TPK) or evisceration. The mean size of the ulcer was 4.84 mm. Ulcer < 4 mm and the presence of hypopyon were associated with treatment failure (p=0.015 and p=0.003, respectively). Vegetative materials were the most common risk factor. *Fusarium species* were isolated from 57.1% of the identified organisms. The most common complications were new corneal infiltrations and hyphemas.
Conclusions: Intrastromal voriconazole injection reduces the need for therapeutic penetrating keratoplasty or evisceration, as approximately one-sixth of patients with non-healing fungal keratitis responded to it.
Keywords: Corneal ulcer, Intracorneal injection, Mycotic keratitis.

***Correspondence Info:**
Dr. Trakanta Wannapanich
KKU Eye Center,
Department of Ophthalmology,
Faculty of Medicine, Srinagarind Hospital,
Khon Kaen University, Thailand

***Article History:**
Received: 01/06/2022
Revised: 26/06/2022
Accepted: 29/06/2022
DOI: https://doi.org/10.7439/ijbr.v13i6.5771

QR Code

How to cite: Wannapanich T and Anutarapongpan O. Treatment outcomes of intrastromal Voriconazole injection for fungal keratitis. *International Journal of Biomedical Research* 2022; 13(6): e5771. DOI: 10.7439/ijbr.v13i6.5771 Available from: https://ssjournals.com/index.php/ijbr/article/view/5771

1. Introduction

Fungal keratitis is a major cause of blindness and usually responds poorly to treatment [1-6]. Voriconazole is a new-generation triazole used for the treatment of fungal corneal ulcers [1,7]. *In vitro* studies have demonstrated its efficacy against filamentous fungi including *Fusarium* spp. [8]. Intrastromal injections have been increasingly used to deliver drugs directly into the cornea. However, results regarding its benefits are still inconclusive due to different study settings and treatment protocols [9-14]. This study aimed to evaluate the outcomes of intrastromal voriconazole injection for the treatment of patients with fungal keratitis resistant to conventional antifungal medication, and report its associated complications.

2. Materials and Methods

We retrospectively reviewed medical records of all patients treated with intrastromal voriconazole injections at a tertiary eye care center between November 2015 and January 2020, and included 70 patients (70 eyes) diagnosed with fungal keratitis in this study. This study was approved by the local institutional ethics committee for human research (HE621051) and carried out according to the Helsinki Declaration of 1975, revised in 2013.

The inclusion criteria were as follows:
(1) Evidence of fungal keratitis by one of the following:
a) Corneal scraping revealing fungal elements in 10% potassium hydroxide mount,
b) Fungus identified from cultures,

c) Polymerase chain reaction (PCR) positive for fungal element (18s rRNA),
d) Histopathological result from corneal button reporting presence of fungus,
e) *In vivo* confocal microscopy of the cornea revealed fungal elements, and
(2) Patients resistant to topical antifungal medications, who underwent intrastromal (intracorneal) voriconazole injection during the treatment course.

We excluded patients with the following conditions:
(1) Concomitant infection in other parts of the eye (i.e., endophthalmitis, scleritis, infectious retinitis),
(2) Coexistence of bacteria reported in culture results, or
(3) History of herpes keratitis.

At the initial presentation, all patients were subjected to the following management. Corneal scraping was performed and the specimen used to obtain the microbiological results, including the fresh smear, cultures (blood agar, chocolate agar, MacConkey agar, Sabouraud dextrose agar), and/or polymerase chain reaction (PCR) to detect fungal elements. *In vivo* confocal microscopy was performed if the diagnostic evaluations were inconclusive. All patients received topical natamycin (5%) (Natacyn; Alcon Labs, Fort Worth, TX) combined with one of the other topical antifungal medications, such as topical voriconazole (1%) (Compounded from Vfend; Pfizer, Inc., New York, NY), topical fluconazole (0.2%) (Compounded from Flucozole; Siam Bheasach Co., Ltd. Bankok, Thailand), topical amphotericin B (0.15%) (Compounded from generic amphotericin B; Sarabhai chemicals, Vadodara 23, India), and topical ketoconazole (2%) (Prepared by adding 2 g of ketoconazole powder and 0.6 g of hydroxypropyl methylcellulose to 100 mL of sterile water). Each topical antifungal medication was administered hourly and then tapered based on clinical response. Some patients received oral itraconazole 200 mg daily divided into two doses (Spornar; Charoen Bhaesaj Lab Co., Ltd. Bangkok, Thailand). We administered intrastromal voriconazole injection if no improvement or progression in terms of the area and depth of the ulcer was observed.

Repeated injections were carried out with a minimum interval of 3 days until the patients reached one of the following endpoints:
1) The infiltration showed improvement with the cornea specialist's decision to taper topical antifungal eye drops less frequently than hourly or
2) Evisceration was considered.

Intracameral voriconazole injection was administered if endothelial plaque or deep fungal infiltrate was present. If the ulcer progressed towards the limbal area, a subconjunctival voriconazole injection was added. Intrastromal, intracameral, and subconjunctival injections could be administered at the same operation if necessary. For patients with uncontrolled extensive infection, including those with corneal perforation or impending perforation, therapeutic penetrating keratoplasty (TPK) or evisceration was considered for clinical judgment by the cornea specialist together with the patient's decision. Keratoplasty techniques depend on the size, severity, and stromal depth of infiltration. Intrastromal voriconazole injections could be administered after TPK if necessary. If infiltration improved, the treatment regimen was tapered, and an outpatient follow-up was scheduled. The treatment endpoint for each patient was met when all forms of antifungal therapy were discontinued without any recurrent infection. The outcome of intrastromal voriconazole injection was considered *"treatment success"* if the corneal infiltration turned into an inactive scar without the need for TPK or evisceration. The others were considered *"treatment failure."*

The data collected included demographic data, possible risk factors, results of microbiological studies, any prior treatment received, presenting clinical findings, initial and final best-corrected visual acuity (BCVA), number of intrastromal voriconazole injections, any complications of the treatment, and clinical outcomes.

2.1 Technique of intrastromal injection

Information regarding the intrastromal injection procedures and possible complications was provided to all patients. We obtained informed consent from all patients before each injection.

Voriconazole 0.5 mg/mL (50 µg/0.1 ml) in 1 ml syringe is locally prepared from injection voriconazole (Vfend; Pfizer, Inc, New York) diluted with lactated Ringer's solution by the hospital pharmaceutical department.

Intrastromal injections of voriconazole were performed under an operating microscope. The procedure included the following steps:
1) Universal standard aseptic technique together with pre-operative anti-bacterial and topical anesthetic eye drops
2) Local anesthetics (2% lidocaine with or without adrenaline) were used (either retrobulbar injection or peribulbar injection)
3) Voriconazole (50 µg/0.1 ml) was injected obliquely into the corneal stroma at four–six points around the infiltration with a 30-gauge needle and allowed to diffuse.

2.2 Statistical Analysis

We analyzed data using the statistical package for the social sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The information was recorded on a data recording form and transferred to an Excel spreadsheet (Microsoft, Redmond, WA, USA). The Snellen visual acuities were converted to the logarithm of the minimum angle of resolution (logMAR) for analysis. Vision levels classified as count

fingers three feet, count fingers two feet, count fingers one foot, and hand motion were assigned equivalent to Snellen acuities of 3/200, 2/200, 1/200, and 2/2000, respectively, similar to a previously published study [15]. The vision levels of light perception and no light perception were not converted to any scale and were described separately. Categorical data were analyzed using *Fisher exact* test, and continuous variables were analyzed using the *t*-test. Statistical significance was set at $p<0.05$.

3. Results

We included 70 patients with fungal keratitis resistant to topical antifungal medications treated with intrastromal voriconazole injection between November 2015 and January 2020 in this study.

3.1 Demographic data and baseline characteristics

Table 1 shows the demographic data and baseline characteristics of patients in this study. Seven patients (10%) had a light-perception vision level at the initial presentation. Hand motion and counting fingers accounted for 60% (n=42) of all patients. For patients with vision better than light perception, the average baseline visual acuity was 1.98 ± 1.09 LogMAR. There was no preference for laterality in the affected eye. Patients with evidence of concomitant bacterial infection were excluded from the study. None of the patients underwent intrastromal antifungal injections before referral to our hospital.

3.2 Treatment outcomes

Of the 61 patients who had complete follow-up, 10 (16.4%) recovered with corneal scarring *(success group)* and 51 (83.6%) needed additional surgical intervention *(failure group)*. Of those who failed the treatment, 26 (42.6%) were cured with TPK and 25 (41.0%) required evisceration. In the evisceration group, 20 of 25 patients underwent prior TPK and 15 patients received intrastromal voriconazole injection post-TPK, but the infection progressed, resulting in evisceration. Nine patients (9/70) were lost to follow-up before reaching the treatment end-point and four were post-TPK. Patients lost to follow-up were excluded from the analysis of the treatment outcomes.

Ulcer size < 4 mm and the presence of hypopyon were associated with treatment failure (p=0.015 and p=0.003, respectively), as shown in Table 1. Six patients (60%) in the *success group* and 10 (19.6%) in the *failure* group had ulcer sizes < 4 mm. Hypopyon was found in 20% (2/10) of patients in the *success group*, which was significantly lower than that in the *failure group (*73% (37/51)). There were no significant differences in the other baseline parameters between both groups.

In the *success group*, all patients (10/10) had an initial BCVA that was better than light perception. In the *failure group*, seven patients (14%) presented with light-perception (LP) vision level, while the other 44 patients had an initial BCVA of 2.16 ± 1.00 LogMAR. Of the patients with LP, five underwent evisceration and two had the same vision level at the end of the treatment. For patients in the *failure group* with initial BCVA better than LP, 20 got blind because of evisceration, three ended with light-perception after TPK, and the remaining 21 cured with TPK had final BCVA of 2.26 ± 1.01 LogMAR (mean difference = 0.31 ± 1.45). Other final characteristics of the patients in the *success group* and the *failure group* are shown in Tables 2 and 3, respectively.

3.2 Adverse events

Of the 248 injections, complications included new corneal infiltration (five patients, 2.0%), hyphema (five patients, 2.0%), new hypopyon (three patients, 1.2%), retrobulbar hemorrhage (two patients, 0.8%), ocular hypertension (two patients, 0.8%), intrastromal air (one patient, 0.4%), and intrastromal foreign body (one patient, 0.4%). Patients with new corneal infiltrations along the injection tract received the same antifungal therapy preoperatively. Post-injection hyphema and hypopyon were minimal, and no anterior chamber irrigation was required. Preoperative retrobulbar anesthesia resulted in retrobulbar hemorrhage in five injections from five patients. All patients were medically managed and resolved by observation, without requiring urgent lateral canthotomy or cantholysis. Ocular hypertension was observed in two patients who underwent intrastromal and intracameral injections in the same operation and were controlled with topical anti-glaucoma eye drops. A patient had small air bubbles inside the corneal stroma postoperatively, as these bubbles were accidentally injected from the syringe during the intrastromal voriconazole injection. Intrastromal air spontaneously resolved the next day without further complications. An intrastromal foreign body (a small piece of thread from a sterile surgical towel) was found in a patient, and the attempt to remove it in the subsequent intrastromal injection was unsuccessful. No stromal reaction or infection was observed during the follow-up period.

Table 1: Baseline characteristics of the patients with recalcitrant fungal keratitis

Variables	Total	Success*	Failure*	*P*-value
Number of patients	70	10 (16.4)	51 (83.6)	
Sex, N (%)				
– Male	48 (68.6)	6 (60.0)	37 (72.5)	
– Female	22 (31.4)	4 (40.0)	14 (27.5)	0.462
Age, Years (Mean ± SD)	52.0 ± 13.3	48.0 ± 16.4	53.0 ± 11.4	0.376
Size, mm (Mean ± SD)	4.84 ± 1.80	4.11 ± 1.50	5.02 ± 1.80	0.133
Size <4mm, N (%)	18 (25.7)	6 (60.0)	10 (19.6)	0.015
Hypopyon, N (%)	43 (61.4)	2 (20.0)	37 (72.5)	0.003
Risk factors, N (%)				
– Vegetative material	38 (54.3)	6 (60.0)	28 (54.9)	1.000
– Soil contamination	21 (30.0)	3 (30.0)	16 (31.4)	0.182
– Contaminated water	2 (2.9)	0 (0.0)	2 (3.9)	1.000
– Eyelash	2 (2.9)	0 (0.0)	2 (3.9)	1.000
– Others	7 (9.9)	1 (10.0)	3 (5.9)	-
Pathogens, N (%)				
– *Fusarium spp.*	25 (35.8)	2 (20.0)	21 (41.2)	0.294
– *Aspergillus spp.*	8 (11.4)	1 (10.0)	4 (7.8)	1.000
– *Lasiodiplodia spp.*	3 (4.3)	0 (0.0)	3 (5.9)	1.000
– *Trichophyton spp.*	2 (2.9)	0 (0.0)	2 (3.9)	1.000
– Other specified	7 (10.0)	1 (10.0)	5 (9.8)	-
– Mixed	3 (6.7)	0 (0.0)	3 (5.9)	-
– Unspecified	25 (35.7)	6 (60.0)	13 (25.5)	-
Injection delay†, Days : Mean‡ ± SD	24.3 ± 11.0	26.4 ± 8.04	25.2 ± 11.3	0.695
Treatment before injection, N (%)				
– Antifungal eye drop (other than voriconazole)	52 (74.3)	8 (80.0)	38 (74.5)	1.000
– Voriconazole eye drop	2 (2.9)	0 (0.0)	2 (3.9)	1.000
– Intracameral antifungals	4 (5.7)	0 (0.0)	4 (7.8)	0.601
– Systemic antifungals§	26 (37.1)	5 (50.0)	19 (37.3)	0.495
– Topical antibiotics	51 (72.9)	9 (90.0)	36 (70.6)	0.267

* Data of the patients who lost to follow-up and who were referred to the other hospitals was excluded
† An average duration from the onset to the first intrastromal voriconazole injection
‡ 1 patient in the *failure group* was excluded since he was previously responsive to treatment in the local hospital (treatment duration 391 days) before the infection was recurrent and the patient was referred.
§ Itraconazole or ketoconazole

Table 2: Final characteristics of the patients in the *success group*

Success group (10)	
Average baseline size of lesion, mm (Mean ± SD)	4.11 ± 1.50
Number of injections per patient, N (Mean ± SD)	3.5 ± 2.5
Average baseline BCVA, LogMAR (Mean ± SD)	1.31 ± 1.22
Final BCVA, LogMAR (Mean ± SD)	0.40 ± 0.31
Final BCVA change from baseline, LogMAR (Mean ± SD)	-0.90 ± 1.04
Outcome duration, days (Mean ± SD)	91.67 ± 38.71

Table 3: Final characteristics of the patients in the *failure group*

TPK and non-evisceration group (26)	
Average baseline size of lesion, mm (Mean ± SD)	4.67 ± 1.64
Number of injections per patient before TPK, N (Mean ± SD)	2.6 ± 2.2
Number of injections per patient after TPK, N (Mean ± SD)	0.5 ± 2.2
Average baseline BCVA, LogMAR (Mean ± SD)	1.91 ± 1.08
Final BCVA, LogMAR (Mean ± SD)	2.23 ± 0.99
Final BCVA change from baseline, LogMAR (Mean ± SD)	0.29 ± 1.38
Outcome duration, days (Mean ± SD)	115.32 ± 37.23
TPK and evisceration group (20)	
Average baseline size of lesion, mm (Mean ± SD)	5.22 ± 1.90
Number of injections per patient before TPK, N (Mean ± SD)	2.4 ± 2.2
Number of injections per patient after TPK, N (Mean ± SD)	2.1 ± 2.6
Outcome duration, days (Mean ± SD)	53.05 ± 31.85
Evisceration group (5)	
Average baseline size of lesion, mm (Mean ± SD)	6.33 ± 2.29
Number of injections per patient, N (Mean ± SD)	10 ± 3.44
Outcome duration, days (Mean ± SD)	10.6 ± 26.34

3. Discussion

Despite current antifungal therapies, fungal keratitis remains a major cause of corneal blindness worldwide. Uncontrolled and extensive infection can result in corneal melting, perforation, or even progression to endophthalmitis. The incidence of fungal keratitis is higher in developing countries, particularly in temperate climate [2-5].

A comparison of baseline characteristics showed that the number of patients with hypopyon at presentation was significantly lower in the *success group*. This finding has been demonstrated in previous studies, although statistical comparison was not performed [9,16]. The mean ulcer size was comparable to that reported in several studies in India [9-11,16]. Moreover, a larger infiltration size was associated with an increased risk of treatment failure, as observed in published studies [9,16]. In our study, the baseline ulcer size in the *failure group* was larger than that in the *success group*. The number of patients whose ulcer size was < 4 mm was significantly lower in the *failure group* according to subgroup analysis. According to Burton *et al*., an infiltrate size > 5 mm was reported to be a risk factor for poor vision and corneal perforation. Although the data for each pathogen were not separately reported in their study, fungal keratitis was present in most participants [17].

The most common risk factor demonstrated in a previous study in developing countries was trauma from agricultural occupation. In contrast, contact lens use and a history of recent ocular surgery are common risk factors in developed countries. In this study, we found that more than half of the patients had a history of vegetative material contamination, which is similar to earlier findings [1,3]. *Fusarium spp.* was the most commonly isolated fungus in developing countries, while yeast was more common in others [2-4]. The results of our study support this finding, as the majority of the identified pathogens were *Fusarium spp*. We did not find any differences in terms of risk factors and causative species between the success and failure groups.

Treatment options for each patient were considered challenging. Factors affecting the drug level at the ulcer site were the route of administration, concentration, and medication contact time [1,18]. Poor penetration of topical antifungal medication is a key limitation, since deep infiltration is characteristic of mycotic keratitis. Thus, targeted delivery of medication by intrastromal injection is performed more frequently, as demonstrated in previous studies [10,12-14,19-22]. The role of the injections is still unclear owing to the limited number of studies. A study on intrastromal natamycin injections reported no additional benefits [23]. Similarly, intrastromal and intracameral injections of amphotericin B were studied and the results showed considerable adverse events, especially anterior chamber reactions [24].

Voriconazole is a recent antifungal medication that has gained interest for ophthalmic applications. Topical voriconazole has a broad-spectrum activity against filamentous fungi and yeast, and is associated with fewer unfavorable events compared with other conventional topical antifungal medications [25]. Intrastromal voriconazole injections have been studied in several case series and interventional clinical trials; however, the outcomes remain inconclusive. In rabbits with *Fusarium* keratitis, Edwar *et al*. reported no statistically significant difference in clinical response between intrastromal voriconazole injection combined with topical voriconazole and topical natamycin monotherapy [26]. Narayana *et al*. conducted a randomized clinical trial and reported no additional benefit of adding intrastromal voriconazole injection to topical natamycin in patients with filamentous fungal keratitis [11]. Their results were explained by the short-lived effect of intrastromal injection, as corneal voriconazole concentration was measured to be very low 6 h post-injection in rats [27]. In contrast, Konar *et al*. [9] concluded that intrastromal voriconazole injection appeared to be effective as adjuvant therapy for recalcitrant fungal keratitis, along with several previous case series [10,14,16,18,28]. Combined intrastromal voriconazole and amphotericin B injections also demonstrated benefits in these patients [29].

Our results showed that approximately one-sixth of fungal keratitis patients resistant to conventional treatment were responsive to intrastromal voriconazole injection. Although some patients with BCVA better than LP could be cured with TPK, 21% of patients (5/24) had the final BCVA turned to LP and the final change in the BCVA among the others in this group tended to be worse than patients cured with corneal scar with the mean difference of 0.29 ± 1.42 LogMAR and -0.90 ± 1.04 LogMAR, respectively. In addition, the findings also suggest that light-perception vision level might be a poor prognostic factor for initiating intrastromal voriconazole injection since none of the patients in this group had a final BCVA better than LP.

The decision to perform these injections requires consideration of their benefits, risks, and complications. In addition to TPK, corneal perforation was the most common adverse event in patients who underwent intrastromal voriconazole injection, followed by secondary glaucoma and hypopyon [11]. In our hospital practice, TPK is usually performed early when progressive corneal melting is observed before corneal perforation occurs. This explains why we did not find any patient with corneal perforation during treatment in our review. New corneal infiltration is a rarely reported complication in literature. All new infections in our study were found along the injection tracts, suggesting that this possibly resulted from needles contaminated with the ulcer during the procedure. Overall,

the complication rate reported in this study was lower than that reported in the literature [11].

This study was limited by its retrospective nature and the lack of a non-intervention group. Treatment regimens varied among patients depending on the presenting clinical status and available resources at the primary hospital prior to referral. Our hospital is a tertiary center; therefore, patients usually present with severe disease. Patients using voriconazole in this trial needed to afford the medication by themselves; thus, the decision to initiate therapy was also limited by the financial situation. Therefore, our findings may represent real-world outcomes of intrastromal voriconazole injections and associated complications. In addition, as mentioned earlier, most infections in this study were related to agricultural activity, and the most common fungal pathogen found was *Fusarium spp.,* which was different from those found in developed countries. Further randomized controlled clinical trials are required to demonstrate the results in a controlled situation.

4. Conclusion

In conclusion, approximately one-sixth of the patients with fungal keratitis resistant to conventional therapy in this study were cured by adjuvant intrastromal voriconazole injection, precluding therapeutic penetrating keratoplasty, or evisceration. The absence of hypopyon at presentation is an important determinant of a successful outcome.

Declarations: The authors declare no conflicts of interest.

Acknowledgements: None

References:

[1]. Ansari Z, Miller D, Galor A. Current Thoughts in Fungal Keratitis: Diagnosis and Treatment. *Curr Fungal Infect Rep* 2013; 7(3): 209–18.

[2]. Bharathi MJ, Ramakrishnan R, Meenakshi R, Padmavathy S, Shivakumar C, Srinivasan M. Microbial Keratitis in South India: Influence of Risk Factors, Climate, and Geographical Variation. *Ophthalmic Epidemiol* 2007; 14(2):61–9.

[3]. Srinivasan M, Gonzales CA, George C, Cevallos V, Mascarenhas JM, Asokan B, *et al*. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, south India. *Br J Ophthalmol* 1997; 81(11): 965–71.

[4]. Ranjini C, Waddepally V. Microbial profile of corneal ulcers in a tertiary care hospital in South India. *J Ophthalmic Vis Res* 2016; 11(4):363.

[5]. Gopinathan U, Sharma S, Garg P, Rao GN. Review of epidemiological features, microbiological diagnosis and treatment outcome of microbial keratitis: Experience of over a decade. *Indian J Ophthalmol* 2009; 57(4):273–9.

[6]. Khor W-B, Prajna VN, Garg P, Mehta JS, Xie L, Liu Z, *et al*. The Asia Cornea Society Infectious Keratitis Study: A Prospective Multicenter Study of Infectious Keratitis in Asia. *Am J Ophthalmol* 2018; 195:161–70.

[7]. Kredics L, Narendran V, Shobana CS, Vágvölgyi C, Manikandan P, Indo-Hungarian Fungal Keratitis Working Group. Filamentous fungal infections of the cornea: a global overview of epidemiology and drug sensitivity. *Mycoses* 2015; 58(4):243–60.

[8]. Marangon FB, Miller D, Giaconi JA, Alfonso EC. In vitro investigation of voriconazole susceptibility for keratitis and endophthalmitis fungal pathogens. *Am J Ophthalmol.* 2004; 137(5):820–5.

[9]. Konar P, Joshi S, Mandhare S, Thakur R, Deshpande M, Dayal A. Intrastromal voriconazole: An adjuvant approach for recalcitrant mycotic keratitis. *Indian J Ophthalmol*. 2020; 68(1):35.

[10]. Prakash G, Sharma N, Goel M, Titiyal JS, Vajpayee RB. Evaluation of Intrastromal Injection of Voriconazole as a Therapeutic Adjunctive for the Management of Deep Recalcitrant Fungal Keratitis. *Am J Ophthalmol* 2008; 146(1):56-59.e2.

[11]. Narayana S, Krishnan T, Ramakrishnan S, Samantaray PP, Austin A, Pickel J, *et al*. Mycotic Antimicrobial Localized Injection. *Ophthalmology.* 2019 Aug; 126(8):1084–9.

[12]. Niki M, Eguchi H, Hayashi Y, Miyamoto T, Hotta F, Mitamura Y. Ineffectiveness of intrastromal voriconazole for filamentous fungal keratitis. *Clin Ophthalmol Auckl NZ* 2014; 8:1075–9.

[13]. Sharma N, Agarwal P, Sinha R, Titiyal JS, Velpandian T, Vajpayee RB. Evaluation of intrastromal voriconazole injection in recalcitrant deep fungal keratitis: case series. *Br J Ophthalmol* 2011; 95(12):1735–7.

[14]. Kalaiselvi G, Narayana S, Krishnan T, Sengupta S. Intrastromal voriconazole for deep recalcitrant fungal keratitis: a case series. *Br J Ophthalmol* 2015; 99(2): 195–8.

[15]. Holladay JT. Visual acuity measurements. *J Cataract Refract Surg*. 2004 Feb; 30(2):287-90.

[16]. Pickel J, Narayana S, Krishnan T, Ramakrishnan S, Samantaray PP, Porco TC, *et al*. The Prognostic Value of Persistent Culture Positivity in Fungal Keratitis in the Mycotic Antimicrobial Localized Injection Trial. *Am J Ophthalmol.* 2020 Jul; 215:1–7.

[17]. Burton MJ, Pithuwa J, Okello E, *et al*. Microbial Keratitis in East Africa: Why are the Outcomes so Poor?. *Ophthalmic Epidemiol*. 2011; 18(4):158-163.

[18]. Kaur IP, Kakkar S. Topical delivery of antifungal agents. *Expert Opin Drug Deliv* 2010; 7(11):1303–27.

[19]. Sun Y, Sun Z, Chen Y, Deng G. Corneal Debridement Combined with Intrastromal Voriconazole for

Recalcitrant Fungal Keratitis. *J Ophthalmol*. 2018; 2018:1-8.

[20]. Sharma N, Chacko J, Velpandian T, Titiyal JS, Sinha R, Satpathy G, *et al*. Comparative Evaluation of Topical versus Intrastromal Voriconazole as an Adjunct to Natamycin in Recalcitrant Fungal Keratitis. *Ophthalmology* 2013; 120(4):677–81.

[21]. Siatiri H, Daneshgar F, Siatiri N, Khodabande A. The Effects of Intrastromal Voriconazole Injection and Topical Voriconazole in the Treatment of Recalcitrant Fusarium Keratitis: *Cornea* 2011; 30(8):872–5.

[22]. Guber I, Bergin C, Majo F. Repeated Intrastromal Injections of Voriconazole in Combination with Corneal Debridement for Recalcitrant Fungal Keratitis – a Case Series. *Klin Monatsbl Augenheilkd* 2016; 233(4):369–72.

[23]. Mimouni M, Tam G, Paitan Y, Kidron D, Segev F. Safety and Efficacy of Intrastromal Injection of 5% Natamycin in Experimental Fusarium Keratitis. *J Ocul Pharmacol Ther* 2014; 30(7):543–7.

[24]. Hu J, Zhang J, Li Y, Han X, Zheng W, Yang J, *et al*. A Combination of Intrastromal and Intracameral Injections of Amphotericin B in the Treatment of Severe Fungal Keratitis. *J Ophthalmol.* 2016; 2016:1-7.

[25]. Hariprasad SM, Mieler WF, Lin TK, Sponsel WE, Graybill JR. Voriconazole in the treatment of fungal eye infections: a review of current literature. *Br J Ophthalmol* 2008; 92(7):871–8.

[26]. Edwar L, Janna YM, Rozaliyani A, Louisa M. Therapeutic response time of topical voriconazole 1% and intrastromal voriconazole 0.05% versus topical natamycin 5% monotherapy in Fusarium keratitis in rabbit. *Mycoses.* 2020; 63(10):1128-1132.

[27]. Gueudry J, Le Goff L, Lamoureux F, *et al*. Corneal Pharmacokinetics of Voriconazole and Posaconazole following Intrastromal Injection and Posaconazole Eye Drops Instillation in Rats. *Curr Eye Res.* 2020; 45(11):1369-1372.

[28]. Agorogiannis EI, Kaye SB, Arbabi E. Intrastromal voriconazole for refractory infectious crystalline keratopathy associated with Candida pararugosa. *Can J Ophthalmol.* Published online March 2021: S0008418221000727.

[29]. Aydin B, Cubuk MO, Ucgul A, *et al*. Combined Intrastromal Voriconazole and Amphotericin B Treatment for Persistent Fungal Keratitis. *Eye Contact Lens*. 2020; 46(5):269-273.