

Effectiveness of Voriconazole in Treating Fungal Keratitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT: Antifungal intervention fails in approximately half of fungal keratitis patients, demonstrating its limitations. Voriconazole use for fungal keratitis has raised new interest because of its broad spectrum and good ocular penetration. However, its effectiveness has not been systematically evaluated. Here we try to clarify the benefits of voriconazole in fungal keratitis cases. Randomized controlled trials (RCTs) comparing voriconazole to placebo or other antifungal medications for fungal keratitis were searched in several databases, including PubMed, Scopus, Cochrane Library, ClinicalTrials, and WHO-ICTRP. The primary outcome that analyzed was best spectacle-corrected vision acuity (BSCVA). The secondary outcomes were treatment success, corneal perforation or need for therapeutic penetrating keratoplasty (TPK). From 621 records, nine studies were selected for analysis. The results were as follows: As an initial therapy, topical natamycin outperformed voriconazole in BSCVA (mean difference = 0.14; 95% CI 0.02 to 0.26; P =.03). Voriconazole also has a greater risk of corneal perforation or TPK than natamycin (RR=1.69; 95% CI 1.11 to 2.58; P=.02). As an adjuvant, there is no significant difference found in BSCVA, treatment success, event of corneal perforation, or need for TPK between voriconazole and the other antifungal agents (itraconazole, ketoconazole, amphotericin B, natamycin, and placebo). This study shows that voriconazole is less superior than natamycin in treating early infections of fungal keratitis. More RCTs with larger samples are needed to evaluate voriconazole's adjuvant efficacy.

Keywords: voriconazole; fungal keratitis; meta-analysis

1. Introduction

In the past decades, the significance of anti-fungal drugs in the practice of modern medicine has increased dramatically [1]. It coincides with an increase in diseases caused by fungal infections, including those affecting the eye organs. Fungal infections of the eye are serious clinical concerns [2]. Keratitis is a leading cause of monocular blindness worldwide; it is estimated that more than half of corneal ulcers in some areas of the world are due to fungus [3–5]. Fungal corneal ulcers are the second most common cause of mono-ocular blindness in developing countries, after cataracts [6]. Both active and resolved infectious keratitis are significant indications of corneal transplantation surgery [7].

Natamycin (NAT) is currently the first-line therapy for fungal keratitis that has been approved by the US Food and Drug Administration and is available in ophthalmic solution. Having a broad spectrum, NAT is usually used as the first choice in *Fusarium* infections, it also has good activity against *Aspergillus*, but less effective in treating *Candida* infection [8]. However, NAT is only available in suspension preparations and has a large molecular size, causing limited penetration into the cornea. Other antifungal agents with a different route of administration are required to cover the NAT limitation in deep-seated keratitis or with involvement of intraocular structures [9].

Voriconazole (VOR) is a newer generation of triazole antifungal agent that has been widely used for fungal infection. The primary mechanism of VOR is inhibition of ergosterol biosynthesis from fungal cells, causing disruption to the function of the fungal plasma membrane, which in turn will inhibit the growth, proliferation, and lysis of fungal cells [10]. VOR has been gaining popularity for treating ocular fungal infections through the topical, oral, and intraocular routes, owing to its broad spectrum activity, high bio-availability, and permeability across the ocular tissues [7,11,12]. It has been proposed as a good

alternative to NAT with minimal toxicity, particularly since susceptibility studies implied that VOR is not only active against filamentous fungi such as *Fusarium* and *Aspergillus*, but also against *Candida* [13–15].

Up to this point, several studies have analyzed and compared the efficacy of VOR to other anti-fungal agents, not only as an initial therapy but also as an adjuvant for treating fungal keratitis. Therefore, we conducted a systematic and meta-analysis study that contribute to evaluate and conclude the studies relevant to this topic.

2. Method

The systematic review was performed according to the reporting guidelines implied by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and the recommendations listed in the Cochrane Handbook [16,17].

2.1. Research question and eligibility criteria

The research question in this study was "the effectiveness of voriconazole therapy in cases of fungal keratitis". The population taken was composed of patients with a diagnosis of fungal keratitis that was proven by direct microscopic examination or culture. Intervention was defined as the administration of VOR in any form compared to a placebo or other types of antifungal agents. We only included randomized controlled trial (RCT) studies with no restrictions on publication date, language, or country. Patients with mixed-infection keratitis were excluded.

2.2. Outcomes analyzed

The primary outcomes of interest were best spectacle-corrected visual acuity (BSCVA) on the final follow-up of the studies reported in log of Minimum Angle of Resolution (logMAR). The secondary outcome discussed in this study were the event of perforation during the study or the need for therapeutic penetrating keratoplasty (TPK), treatment success indicated by complete

reepithelialization, resolution of corneal infiltrate, and no hypopyon found.

2.3. Search strategy and studies selection

Studies were searched from five electronic databases, Medline via PubMed, Scopus, Cochrane Library, ClinicalTrials, and WHO-ICTRP. The last search was conducted on September 26th, 2022. One reviewer (Y.A.A.) developed a search strategy using relevant keywords and using medical subject headings (MeSH) in the form of "eye infections", "keratitis", "fungal keratitis", "mycotic keratitis", "mycotic", "keratomyco*", "filament*", "candida keratitis", "corneal ulcer", "antifungal agents", "antifungal", "voriconazole", "natamycin", "ketoconazole", "iconazole", "fluconazole", "posaconazole", "itraconazole", "amphotericin b", "caspofungin", "micafungin", "random*". Search results were pooled, and duplicates were removed.

2.4. Data extraction

Two reviewers independently performed data extraction (Y.A.A., E.A.I.). If the data were unavailable, we contacted the authors via email. We followed up with the initial email if no reply was received after one week. Data extracted were country, study length, sample size and age distribution of the population, antifungal agents used, dosage, and reported outcome. The process of duplication removal and study extraction was carried out using the online software, DistillerSR.

2.5 Risk of bias assessment

Two reviewers (Y.A.A., E.A.I.) used the Cochrane tool for assessing the risk of bias in randomized trials (RoB 2) independently [18]. Five domains of bias were assessed: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results. At the end of the judgment, there would be an overall bias. A study with a low risk of bias in all five previous domains was categorized as having a low risk of bias in the overall bias domain.

If only one domain has some concerns, there was no high risk of bias in any domain. High risk of bias in the study was judged to be at high risk of bias in at least one domain or if some concerns appear in multiple domains.

2.6 Results and statistical analysis

The extracted data were analyzed using Review Manager for Macbook (RevMan version 5.4.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), and forest plots were prepared. Continuous data used for meta-analysis that were presented as median and interquartile range were converted to mean and standard deviation with a calculator in RevMan version 5.4.1. The Mantel-Haenszel random-effects model was used to calculate the risk ratio (RR) and weighted mean difference (WMD), and 95 percent confidence intervals (95% CI) were used. Study heterogeneity was quantified using the I_2 statistic, which was assessed according to the following criteria: I_2 less than 25 percent, no heterogeneity; I_2 of 25–50 percent, moderate heterogeneity; and I_2 greater than 50 percent, high heterogeneity. A P -value of less than 0.050 indicated a significant difference.

3. Results and discussions

3.1. Study identification

We found 621 articles in the five electronic databases mentioned earlier. After removing duplicates, we screened the titles and abstracts of 427 articles, of which 401 were excluded because they did not meet the criteria of our study. Twenty-six articles were retrieved for full-text review, with 17 being excluded for various reasons. We included nine studies for qualitative synthesis, but only four of them could be meta-analyzed as shown in Figure 1.

3.2 Characteristics of included studies

Table 1 summarized the characteristics of the included studies. Eight of the RCTs included were conducted in India, and one was a joint study

from India and Nepal. The total number of subjects retrieved from all the studies was 1056 participants.

Five studies analyzed topical VOR [19–23]; three studies analyzed oral VOR [21,24,25]; and two studies analyzed intrastromal VOR [26,27], and they were compared with other antifungal agents. The dosage regimen used in each study was not significantly different. VOR eye drop 1% was used every 1 to 2 hours per day. For oral

preparations, a loading dose of 400mg was used two times per day, followed by 200mg the next day. Only one study used a dose of 200mg since the first day [25]. VOR intrastromal concentration 50µg/0.1 mL was used. The studies' follow-up periods range from 21 days to 6 months.

3.3 Risk of bias assessment

The results of the risk of bias assessment can be seen in Figure 2. In overall bias, there are three

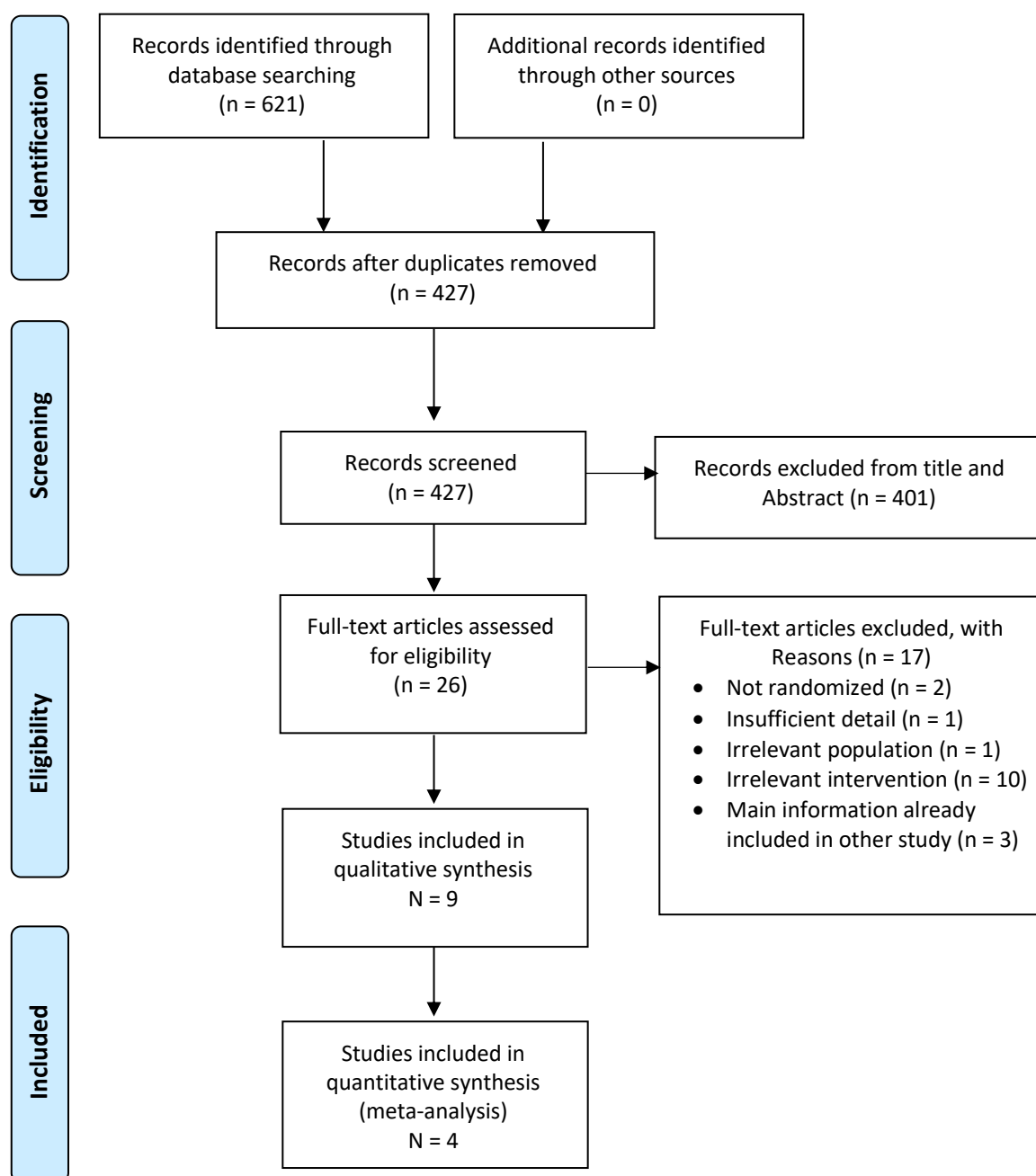


Figure 1. PRISMA flow diagram of the selection process of articles for meta-analysis

Table 1. Characteristics of studies included in the present review

Study/ Country	Sample Size	Mean Age	Intervention and Comparison	Dosage	Outcome
Prajna, 2010 ²⁰ / India	120	46.9	VOR 1% NAT 5%	NAT 5% and VOR1%: q.1.h. on 1st week, q.2.h. on 2nd and 3rd week [*]	Assesment in 3 weeks and 3 months on - BSCVA - clinical characteristics (infiltrate/scar size, epithelial defect size)
Arora, 2011 ²¹ / India	30	43.1	VOR 1% NAT 5%	NAT 5% and VOR1%: q.1.h. for 2 weeks, then tITRted according to the patient's response	- Time taken for the complete resolution of the ulcer - BSCVA and size of ulcer and hyopion at week 1, 2, 4 and final visit
Parchand, 2012 ²² / India	45	> 18	VOR 1% + VOR 200mg NAT 5% + VOR 200mg NAT 5% + ITR 200mg	- VOR 200mg: day one 400mg b.i.d., followed by 200mg b.i.d. - ITR 200mg: b.i.d. - VOR 1%: q.1.h. - NAT 5%: q.1.h.	- Time to resolution of epithelial defect, infiltrates, and hypopyon (if present) - Corneal opacity and BSCVA at 3 months
Prajna, 2013 ²³ / India	323	47	VOR 1% NAT 5%	NAT 5% and VOR1%: q.1.h. on 1st week, q.2.h. on 2nd and 3rd week	- BSCVA at 3 weeks and 3 months - Scar size at 3 weeks and 3 months - Time to reepithelialization - microbiological cure at 6 days - corneal perforation and/or TPK
S. Sharma, 2015 ²⁴ / India	118	41	VOR 1% NAT 5%	NAT 5% and VOR1%: Day 1-3: q.1.h. Day 4: q.1.h. while awake, q.3.h. when asleep Day 5 onward: q.2.h. while awake until cured.	Assessment in 1 week and last visit on - Response to medical treatment - BSCVA - Evaluate the relationship between the final visual acuity to fungal species, drug, follow-up, age, gender, mean corneal infiltrate size and mean size of corneal epithelial defect
Prajna, 2016 ¹⁹ / India and Nepal	240	52	NAT 5% + VOR 1% + VOR 200mg NAT 5% + VOR 1% + Placebo	- VOR 200mg: day one 400mg b.i.d., followed by 200mg b.i.d. (20 days) - NAT 5% and VOR1%: q.1.h. on 1st week, q.2.h. on 2nd and 3rd week	- Perforation or the need for TPK within 3 months - BSCVA at 3 weeks and 3 months - Infiltrate and/or scar size at 3 weeks and 3 months - Time to re- epithelialization - Microbiologic cure at 6 days (± 1 day) - Complications
N. Sharma, 2017 ²⁵ / India	50	47.4	NAT 5% + VOR 200mg NAT 5% + KET 200mg	- NAT 5%: q.1.h. for 2 days, then q.2.h until epithelial healing, then q.4.h. for 3 weeks - KET 200mg: q.2.d.	- BSCVA at 3 months. - Percentage of healed cases in each group and scar size
Narayana, 2019 ²⁶ / India	70	54	NAT 5% + VOR 50 μ g/0.1 mL NAT 5%	- NAT 5%: q.1.h. - VOR 50 μ g/0.1 mL: at day 1, 3, and 5	- Microbiological cure on 3 and 7 days repeat culture - BSCVA at 3 weeks and 3 months - Infiltrate and/or scar size - Rate of perforation and TPK - Adverse events
Saluja, 2021 ²⁷ / India	60	41.1	NAT 5% + VOR 50 μ g/0.1 mL NAT 5% + AMB 50 μ g/0.1 mL	- NAT 5%: q.2.h. - VOR 50 μ g/0.1 mL, AMB 5 μ g/0.1 mL, and NAT(dosage not stated): 1 to 3 times, q.72.h.	- Time taken till complete clinical resolution of infection - Treatment success - BSCVA at 6 months - Complications

VOR=voriconazole, NAT=natamycin, ITR=itraconazole, KET=ketoconazole, AMB=amphotericin B
BSCVA=best spectacle-corrected visual acuity, TPK= theurapetic penetrating keratoplasty

studies with low risk [19,24,27], two studies with some concern [22,23], and four studies with a high risk of bias [20,21,25,26].




3.4 Quantitative synthesis (meta-analysis)

The most frequently compared group was topical 1% VOR and 5% NAT, where they used as

an initial treatment to fungal keratitis. We conducted a meta-analysis of the four studies comparing these two agents [21,23,25,27]. Clinical improvement was measured based on BSCVA improvement and treatment success. While corneal perforation or the need for TPK indicate treatment failure.

	A	B	C	D	E	F
Arora <i>et al</i> 2011	?	+	+	+	?	-
Narayana <i>et al</i> 2019	+	-	?	+	+	-
N Sharma <i>et al</i> 2017	+	?	+	+	?	-
Parchand <i>et al</i> 2012	?	?	+	-	?	-
Prajna <i>et al</i> 2010	+	+	+	+	+	+
Prajna <i>et al</i> 2013	+	?	+	+	+	?
Prajna <i>et al</i> 2016	+	+	+	+	+	+
Saluja <i>et al</i> 2021	+	+	+	+	+	+
S Sharma <i>et al</i> 2015	+	?	+	+	+	?

Judgement:

-  High risk
-  Some concern
-  Low risk

Domains:

- A: Bias arising from the randomization process
- B: Bias due to deviations from intended interventions
- C: Bias due to missing outcome data
- D: Bias in measurement of the outcome
- E: Bias in selection of the reported result
- F: Overall bias

Figure 2. Risk of bias assessment for each selected study

BSCVA outcome. Only three studies could be synthesized for meta-analysis on BSCVA outcome. Two studies from Prajna *et al.* reported BSCVA three months after treatment [19,22], while Arora *et al.* reported BSCVA on the final visit [20]. We found that NAT significantly gave a better results in BSCVA compared to VOR (mean difference=0.14; 95% CI 0.02 to 0.26; $P=0.03$; $I^2=30\%$) (Figure 3).

Corneal perforation and need for TPK. All nine studies reported the number of corneal perforations during the studies [19–27]. Meta-analysis on four studies compared topical 1% VOR and 5% NAT showed some evidence that VOR has a higher risk of corneal perforation or the need for TPK (RR=1.69; 95% CI 1.11 to 2.58; $P=0.02$; $I^2=0\%$) (Figure 4) [19,20,22,23].

Treatment success. No meta-analysis could be performed because all three studies that met

our treatment success criteria had a different comparison group [21,23,27].

According to the outcome of the meta-analysis, VOR did not show superior results compared to NAT (Figure 2 and 3). The studies compared VOR and NAT as the initial and sole therapy for fungal keratitis infection. *Fusarium* was identified as the most common fungus causing keratitis in three of the four studies included in the meta-analysis [19,22,23]. Previous studies showed that *Fusarium* isolates were less susceptible to VOR than to NAT. High MICs for antifungals are needed to treat *Fusarium* species in general, especially for VOR. This result was consistent in vitro studies as well as in vivo studies [28–31]. Other fungi, including *Aspergillus* and *Candida* species, are more susceptible than *Fusarium* species to azoles, particularly VOR [31].

Several studies have shown that an individu-

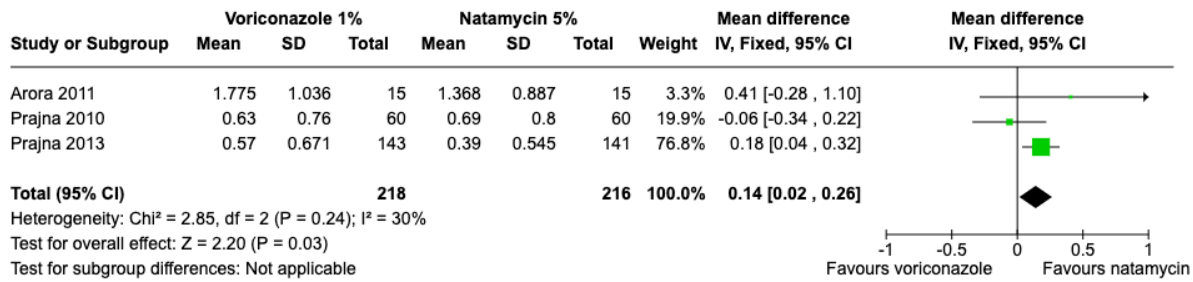


Figure 3. The results of the meta-analysis on primary outcomes for best spectacle-corrected visual acuity. CI (confidence interval), SD (standard deviation)

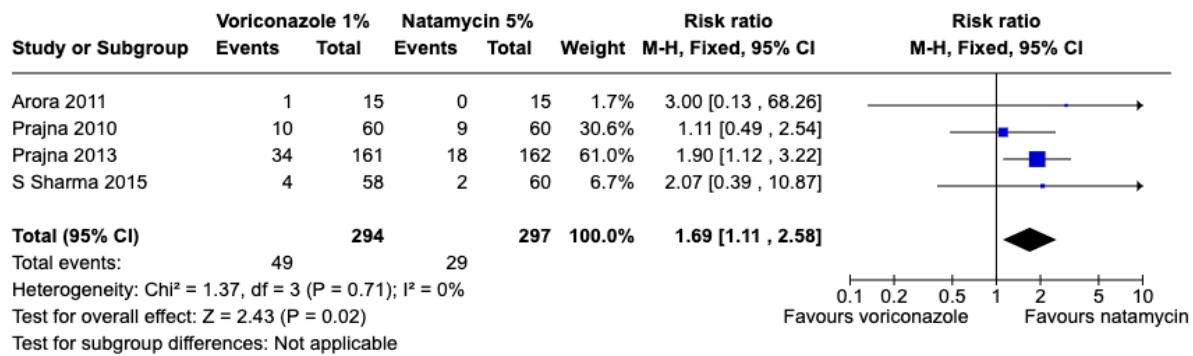


Figure 4. The results of the meta-analysis on secondary outcomes for the event of perforation during the study or the need for therapeutic penetrating keratoplasty. CI (confidence interval)

al's ability to metabolize drugs via the CYP2C19 P450 enzyme influences the pharmacokinetic variability of VOR. Polymorphisms in the gene encoding this enzyme are common, resulting in variable VOR metabolism rates. This polymorphism differs across races, with Caucasians having greater metabolic ability than Asians. Decreased metabolism or absorption related to genetic factors or drug interactions may result in insufficient exposure of the treatment to the fungal pathogen [32]. The majority of the studies examined in this study took place in India, a tropical and developing country where fungal keratitis is usually common. Based on the theory above, these studies findings could likely to differ in other locations where the majority of subjects are Caucasian. However, we haven't found any comparative study on VOR conducted in any country other than one in Asian region. It is understandable because the urgency to conduct a study on fungal keratitis is low because it is less common in temperate and developing countries,

where the majority of Caucasians live. It showed from the report from recent systematic review that estimated annual incidence ranged from 73 per 100,000 in South Asia to just 0.02 per 100,000 in Europe [33].

3.5 Qualitative synthesis

The qualitative synthesis only described the findings of the included studies that analyzed and compared VOR to other antifungal agents. Due to the limited number of RCT studies and for most comparisons only one small trial was available, the data could not be meta-analyzed further to improve statistical power. There were five studies with different VOR comparison groups [21,24–27]. All five studies evaluated VOR in oral or intrastromal injection form as the adjuvant to the primary treatment, which was topical NAT. The specific details of the outcomes from the studies are presented in Table 2.

BSCVA outcome. Two studies compared oral VOR with placebo; and oral VOR with oral KET,

Table 2. Outcomes from included studies

Study	Intervention	Follow up time	Subject	Corneal perforation/need for TPK		Best Corrected Spectacle Visual Acuity in logMAR		Treatment Success	
				N	Statistical Outcome	Mean (SD) or Median (IQR)	Statistical Outcome	N	Statistical Outcome
Prajna, 2010 ³⁰	VOR 1%	3 months	60	10	NA	0.63 (0.76)	VOR had 0.098 better logMAR acuity (nearly 1-line benefit) (95% CI, -0.28 to 0.083; P=.29)	NA	NA
	NAT 5%	60	9			0.69 (0.80)		NA	
Arora, 2011 ²¹	VOR 1%	Last follow up	15	1	NA	1.368 (0.887)	No significant difference between two groups (P=.227)	14	NA
	NAT 5%	15	0			1.775 (1.036)		15	
Parchand, 2012 ²²	VOR 1% + VOR 200mg	3 months	15	5	NA	1.7 (0.9)	NA	10	No significant difference between three groups (P=.902)
	NAT 5% + VOR 200mg	15	4			1.5 (0.8)		11	
Prajna, 2013 ²³	NAT 5% + ITR 200mg	15	5			1.2 (0.6)		10	
	VOR 1%	3 months	161	34	NAT less likely to undergo perforation or TPK (OR=0.42; 95% CI, 0.22 to 0.80; P=.009)	0.57 (0.46-0.68)	VOR had 1.8 lines worse (regression coefficient = -0.18 logMAR; 95% CI, -0.30 to -0.05; P = .006)	NA	NA
NAT 5%	NAT 5%	162	18			0.39 (0.30-0.48)		NA	
	VOR 1%	58	4			NA	NA	34	NAT had significantly higher rate of healed corneal ulcer (P=.005)
S. Sharma, 2015 ²⁴	NAT 5%	60	2			NA	NA	50	
Prajna, 2016 ¹⁹	NAT 5% + VOR 1% + VOR 200mg	3 months	119	49	VOR decreased risk for perforation or need for TPK (HR=0.82; 95% CI, 0.57 to 1.18; P=.29)	1.26 (0.61)	No significant difference between two groups	NA	NA
	NAT 5% + VOR 1% + Placebo	121	56			1.30 (0.61)	(predicted BSCVA, -0.02 logMAR; 95% CI, -0.18 to 0.14; P=.77)	NA	NA
N. Sharma, 2017 ²⁵	NAT 5% + VOR 200mg	3 months	27	3	No significant difference between two groups (P=.70)	1.3 (0.35)	VOR had 0.26 better logMAR acuity (95% CI, 0.04-0.48; P=.02)	20	No significant difference between two groups (95% CI, 20.15 to 0.31; P=0.51)
	NAT 5% + KET 200mg	27	5			1.6 (0.39)		18	
Narayana, 2019 ²⁶	NAT 5% + VOR 50µg/0.1 mL	3 months	35	14	VOR had relative hazard of 0.95 for eventuating to TPK (95% CI, 0.44 to 2.04; P=.90)	1.30	VOR had 0.5 worse logMAR acuity (approx. 1/2 Snellen line) (95% CI, -2.6 to 3.6; P=.75)	NA	NA
	NAT 5%	35	13			1.28 (0.66)		NA	
Saluja, 2021 ²⁷	NAT 5% + VOR 50µg/0.1 mL	6 months	20	1	NA	1.2 (0.38)	No significant difference between three groups (P=.54)	19	No significant difference between three groups (P=.8)
	NAT 5% + AMB 50µg/0.1 mL	20	2			1.35 (0.47)		18	
NAT 5% + NAT intrastromal	20	1				1.2 (0.37)		19	

VOR=voriconazole, NAT=natamycin, ITR=itraconazole, KET=ketoconazole, AMB=amphotericin B
 N=number (frequency), NA=not analyzed, SD=standard deviation, IQR=interquartil range, TPK=theurapetic penetrating keratoplasty, CI=confidence interval, OR=odds ratio, HR=hazard ratio

and the results stated there were no significant difference found (95% CI, -0.18 to 0.14; $P=0.77$) and 0.26 better logMAR acuity in VOR group (95% CI, 0.04–0.48; $P=0.02$) respectively [24,25]. As an intrastromal injection adjuvant, VOR had no significant difference when compared to topical NAT alone (95% CI, -2.6 to 3.6; $P=0.75$) and when compared to intrastromal AMB and intrastromal NAT ($P=0.54$) [26,27].

Corneal perforation and need for TPK. In the MUTT II study, although the result is not statistically significant, oral VOR reduced the risk for perforation or need for TPK when compared to placebo (HR=0.82; 95% CI, 0.57 to 1.18; $P=0.29$) [24]. There was also no significant difference in the event of corneal perforation of oral VOR and oral KET ($P=0.70$) [25]. In intrastromal injection form, VOR had a relative hazard of 0.95 for eventuating to TPK versus group with topical NAT alone (95% CI, 0.44 to 2.04; $P=0.90$). [26] Other studies stated the number of corneal perforation rates but did not do statistical analysis (Table 2) [21,27].

Treatment success. Of the four studies [21,23,25,27] that reported treatment success, three of them met our success criteria [21,23,27]. Sharma et al. found that the percentage of patients receiving NAT was significantly more successful than VOR ($P=0.005$) [23]. More than 90% success was found in all intrastromal VOR, AMB, and NAT groups, but there was no significant difference between the three groups ($P=0.80$) [27]. Parch shown et al. also reported no significant difference shown between the success of the VOR, NAT, or itraconazole (ITR) groups ($P=0.90$) [21].

All studies in the qualitative synthesis section evaluated the role of VOR as an adjuvant therapy to topical NAT. In the oral forms, VOR was compared with oral KET, oral ITR, and placebo [21,24,25]. The majority of the results indicated that VOR has the same efficacy as the other antifungal agents, with no significant difference found in BSCVA, event of corneal perforation or need for TPK, or treatment success, except for a statistically better BSCVA outcome in the oral

VOR group when compared to the oral KET [25]. It should be noted that two of the studies analyzing the efficacy of oral VOR compared to KET and ITR had a small number of subjects with an overall high-risk of bias [21,25].

In a secondary analysis of the MUTT II study, Parchand et al. discovered that *Fusarium* ulcers randomized to treatment with oral VOR in addition to topical NAT and VOR had a lower rate of corneal perforation, smaller scar size, and more rapid reepithelialization [34]. This finding is supported by another study that found that the synergistic action of NAT and VOR resulted in more effective antifungal activity than single-use in vitro treatment in all species tested, implying that these combinations may be useful in the management of fungal keratitis [35].

The efficacy of non-topically administered medications in ocular disease depends on the ability of the drug to cross the blood-ocular barriers, specifically the blood-aqueous barrier during anterior segment disease [36]. Hariprasada et al. reported that orally administered VOR achieves therapeutic aqueous and vitreous levels in the non-inflamed human eye [37]. The concentration of oral VOR obtained from the vitreous in non-inflamed eyes 12 hours after administration exceeds the MIC90 for a wide range of yeasts and molds, but not for *Fusarium* species [38]. However, in an inflammatory state, as occurs secondary to corneal disease, capillaries become more permeable, allowing substances that are normally excluded from the blood-aqueous barrier to enter the anterior chamber, which could potentially have a therapeutic effect [36].

The selection of antifungals in the clinical setting, particularly when administered systemically, must be adjusted to the patient's condition. The significant toxicity of KET and ITR limits their systemic use in patients with hepatic problems. Hepatotoxicity and liver failure are the most common and serious adverse effects. Therefore, VOR could be a better option because it has milder adverse effects, such as visual disturbances, color vision changes, and photophobia,

which usually subside after 30 minutes [39].

Two studies comparing intrastromal VOR adjuvant to topical NAT alone and other intrastromal adjuvants such as AMB and NAT found no statistically significant difference in any of the three outcomes studied [26,27].

Intrastromal injection may be an effective method of administering antifungal agents. It is capable of increasing local concentrations and is sufficiently effective in eradicating deep corneal infections [40]. However, animal studies revealed that the aqueous humor concentration of VOR decreased rapidly following intrastromal and intracameral injection [41,42]. The decline of VOR in aqueous concentration shows an exponential decay with a half-life of 22 minutes. Although the pharmacodynamics of intrastromal VOR are unknown, these findings suggest that a sufficient level of VOR in the corneal stroma may not be maintained for long after the injection [41]. This might be happened because rapid triazole diffusion was facilitated by low molecular weight for the partially hydrophilic VOR. It contrasts with AMB which has a high molecular weight, where the concentration of intrastromal injection could last above MICs of most fungi for 7 days [42,43].

3.6. Study Limitations

This study has several limitations, one of which is the lack of a study comparison for adjuvant VOR, which limits future analysis. Furthermore, the reporting of outcomes of fungal keratitis treatment is insufficiently standardized, preventing the synthesis of results across studies, despite the fact that there is currently no specific guideline for reporting keratitis studies available. We also do not examine other clinically significant outcomes, such as time to resolution or re-epithelialization, scar size, and complications.

Overall, only a few of the studies analyzed have a low overall risk of bias, which may affect the validity of the results presented. More research is needed to obtain more robust evidence on the benefits of VOR, particularly as an adjuvant therapy, by conducting an RCT with good randomiza-

tion, follow-up, intention-to-treat analysis, and presenting a complete study outcome. Because each antifungal agent has a unique spectrum of antifungal activity, subgroup analysis of specific antifungal etiologies should be performed to identify the treatment effect.

4. Conclusion

In conclusion, the current study shows that VOR is less effective as an early treatment than NAT, which is still the first-line therapy for fungal keratitis. More large and well-designed RCTs are needed to confirm VOR's efficacy, particularly as adjuvant therapy in the treatment of deep fungal keratitis or keratitis that does not respond well to first-line therapy.

Competing interests

We declared that all authors have no competing interests to declare.

References

1. Roemer T, Krysan DJ. Antifungal drug development: Challenges, unmet clinical needs, and new approaches. *Cold Spring Harbor perspectives in medicine*. 2014;4.
2. Patil A, Majumdar S. Echinocandins in ocular therapeutics. *Journal of Ocular Pharmacology and Therapeutics*. 2017;33:340–52.
3. Sharma N, Sankaran P, Agarwal T, Arora T, Chawla B, Titiyal JS, et al. Evaluation of intracameral Amphotericin B in the management of fungal keratitis: Randomized controlled trial. *Ocul Immunol Inflamm*. 2016;24(5):493–7.
4. Joseph J, Sharma S. Antifungal therapy in eye infections: New drugs, new trends. In: *Recent trends in antifungal agents and antifungal therapy*. Springer India; 2016:217–36.
5. Lalitha P, Shapiro BL, Srinivasan M, Ruiz J, Chi-

- dambaram JD, Maxey KJ, et al. Antimicrobial susceptibility of *Fusarium*, *Aspergillus*, and other filamentous fungi isolated from keratitis. *Arch Ophthalmol*. 2007;125.
6. Gupta MK, Chandra A, Prakash P, Tilak R. Necessity to identify the causative agent for appropriate treatment in fungal corneal ulcer: an in vitro study. *J Mycol Med*. 2018;28(1):201–5.
 7. Benhamou RI, Bibi M, Steinbuch KB, Engel H, Levin M, Roichman Y, et al. Real-Time imaging of the azole class of antifungal drugs in live *Candida* cells. *ACS Chem Biol*. 2017;12(7):1769–77.
 8. Suman S, Kumar A, Saxena I, Kumar M. Fungal keratitis: Recent advances in diagnosis and treatment. In: *Infectious Eye Diseases - Recent Advances in Diagnosis and Treatment*. IntechOpen;2021.
 9. Neoh CF, Daniell M, Chen SCA, Stewart K, Kong DCM. Clinical utility of caspofungin eye drops in fungal keratitis. *International Journal of Antimicrobial Agents*. 2014;44:96–104.
 10. Gubert Müller G, Kara-José N, Silvestre De Castro R. Antifungals in eye infections: drugs and routes of administration. Antifúngicos em infecções oculares: drogas e vias de administração. *Rev Bras Oftalmol*. 2013;72(2):132–41.
 11. Thakkar R, Patil A, Mehraj T, Dudhipala N, Majumdar S. Updates in ocular antifungal pharmacotherapy: Formulation and clinical perspectives. *Current Fungal Infection Reports*. 2019;13:45–58.
 12. Malhotra S, Khare A, Grover K, Singh I, Pawar P. Design and evaluation of voriconazole eye drops for the treatment of fungal keratitis. *J Pharm (Cairo)*. 2014:1–9.
 13. Ansari Z, Miller D, Galor A. Current thoughts in fungal keratitis: Diagnosis and treatment. *Curr Fungal Infect Rep*. 2013;7(3):209–18.
 14. Atta S, Perera C, Kowalski RP, Jhanji V. Fungal keratitis: Clinical features, risk factors, treatment, and outcomes. *Journal of Fungi*. 2022;8(9).
 15. Das S, Mitra S, Garg P, Mallick A, Priyadarshini S, Sharma S. Efficacy of Voriconazole and Amphotericin B in corneal preservative media. *Indian J Ophthalmol*. 2022;70(1):90–4.
 16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Vol. 372. BMJ Publishing Group; 2021.
 17. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane; 2022.
 18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *The BMJ*. 2019:366.
 19. Prajna N v., Mascarenhas J, Krishnan T, Reddy PR, Prajna L, Srinivasan M, et al. Comparison of natamycin and voriconazole for the treatment of fungal keratitis. *Archives of Ophthalmology*. 2010;128(6):672–8.
 20. Arora R, Gupta D, Goyal J, Kaur R. Voriconazole versus natamycin as primary treatment in fungal corneal ulcers. *Clin Exp Ophthalmol*. 2011;39(5):434–40.
 21. Parchand S, Gupta A, Ram J, Gupta N, Chakrabarty A. Voriconazole for fungal corneal ulcers. *Ophthalmology*. 2012;119.
 22. Venkatesh Prajna N, Krishnan T, Mascarenhas J, Rajaraman R, Prajna L, Srinivasan M, et al. The mycotic ulcer treatment trial: A randomized trial comparing Natamycin vs Voriconazole. *JAMA Ophthalmol*. 2013;131.
 23. Sharma S, Das S, Virdi A, Fernandes M, Sahu SK, Koday NK, et al. Re-appraisal of topical 1% voriconazole and 5% natamycin in the treatment of fungal keratitis in a randomised trial. *Br J Ophthalmol*. 2015:1–6. Available from: <http://bjo.bmj.com>
 24. Prajna NV, Krishnan T, Rajaraman R, Patel S, Srinivasan M, Das M, et al. Effect of oral voriconazole on fungal keratitis in the Mycotic Ulcer Treatment Trial II (MUTT II): A randomized clinical trial. *JAMA Ophthalmol*. 2016;134(12):1365–72.
 25. Sharma N, Singhal D, Maharana PK, Sinha R, Agarwal T, Upadhyay AD, et al. Comparison of oral voriconazole versus oral ketoconazole as an adjunct to topical natamycin in severe fungal keratitis: A randomized controlled trial. 2017. Available from: www.corneajrnl.com
 26. Narayana S, Krishnan T, Ramakrishnan S, Saman-

- taray PP, Austin A, Pickel J, et al. Mycotic antimicrobial localized injection: A randomized clinical trial evaluating intrastromal injection of voriconazole. *Ophthalmology*. 2019;126(8):1084–9.
27. Saluja G, Sharma N, Agarwal R, Sharma HP, Singhal D, Maharana PK, et al. Comparison of safety and efficacy of intrastromal injections of voriconazole, amphotericin B and natamycin in cases of recalcitrant fungal keratitis: A randomized controlled trial. *Clinical Ophthalmology*. 2021;15:2437–46.
28. Lalitha P, Sun CQ, Prajna NV, Karpagam R, Geetha M, O'Brien KS, et al. In vitro susceptibility of filamentous fungal isolates from a corneal ulcer clinical trial. *Am J Ophthalmol*. 2014;157(2):318–26.
29. Szaliński M, Zgryźniak A, Rubisz I, Gajdzis M, Kaczmarek R, Przędziecka-dołyk J. Fusarium keratitis—review of current treatment possibilities. *Journal of Clinical Medicine*. 2021;10.
30. Gajjar DU, Pal AK, Ghodadra BK, Vasavada AR. Microscopic evaluation, molecular identification, antifungal susceptibility, and clinical outcomes in Fusarium, Aspergillus and, dematiaceous keratitis. *Biomed Res Int*. 2013;2013.
31. Oechsler RA, Yamanaka TM, Bispo PJM, Sartori J, Yu MCZ, Melo ASA, et al. Fusarium keratitis in Brazil: Genotyping, in vitro susceptibilities, and clinical outcomes. *Clinical Ophthalmology*. 2013;7:1693–701.
32. Girmenia C, Finolezzi E. New-generation triazole antifungal drugs: review of the Phase II and III trials. *Clin Investig (Lond)*. 2011;1(11):1577–94.
33. Brown L, Kamwiziku G, Oladele RO, Burton MJ, Prajna NV, Leitman TM, et al. The case for fungal keratitis to be accepted as a neglected tropical disease. *Journal of Fungi*. 2022;8.
34. Prajna NV, Krishnan T, Rajaraman R, Patel S, Shah R, Srinivasan M, et al. Adjunctive oral voriconazole treatment of Fusarium keratitis: A secondary analysis from the Mycotic Ulcer Treatment Trial II. *JAMA Ophthalmol*. 2017;135(6):520–5.
35. Sradhanjali S, Yein B, Sharma S, Das S. In vitro synergy of natamycin and voriconazole against clinical isolates of *Fusarium*, *Candida*, *Aspergillus* and *Curvularia* spp. *British Journal of Ophthalmology*. 2018;102(1):142–5.
36. Clode AB, Davis JL, Salmon J, Michau TM, Gilger BC. Evaluation of concentration of voriconazole in aqueous humor after topical and oral administration in horses. *AJVR*. 2006;67(2):296–301.
37. Hariprasad SM, Mieler WF, Lin TK, Sponsel WE, Graybill JR. Voriconazole in the treatment of fungal eye infections: A review of current literature. *British Journal of Ophthalmology*. 2008;92(7):871–8.
38. Hariprasad SM, Mieler WF, Holz ER, Gao H, Kim JE, Chi J, et al. Determination of vitreous, aqueous, and plasma concentration of orally administered voriconazole in humans. *Arch Ophthalmol*. 2004;122.
39. Sahay P, Singhal D, Nagpal R, Maharana PK, Farid M, Gelman R, et al. Pharmacologic therapy of mycotic keratitis. *Survey of Ophthalmology*. 2019;64:380–400.
40. 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):1128–32.
41. Niki M, Eguchi H, Hayashi Y, Miyamoto T, Hotta F, Mitamura Y. Ineffectiveness of intrastromal voriconazole for filamentous fungal keratitis. *Clinical Ophthalmology*. 2014;8:1075–9.
42. Guedry J, le Goff L, Lamoureux F, Pereira T, Levefre S, Razakandrainibe R, et al. Corneal pharmacokinetics of voriconazole and posaconazole following intrastromal injection and posaconazole eye drops instillation in rats. *Curr Eye Res*. 2020;1–4.
43. Qu L, Li L, Xie H. Corneal and aqueous humor concentrations of amphotericin B using three different routes of administration in a rabbit model. *Ophthalmic Res*. 2010;43(3):153–8.