Adjunctive Oral Voriconazole Treatment of *Fusarium* Keratitis: A Secondary Analysis From the Mycotic Ulcer Treatment Trial II

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**IMPORTANCE** *Fusarium* keratitis is common and often results in poor outcomes. No new treatments since natamycin have become available.

**OBJECTIVE** To explore the role of adjuvant oral voriconazole on clinical outcomes in *Fusarium* keratitis.

**DESIGN, SETTING, AND PARTICIPANTS** In this prespecified subgroup analysis of a multicenter, double-masked, placebo-controlled randomized clinical trial, 240 patients from the Aravind Eye Care System in India, the Lumbini Eye Hospital and Bharatpur Eye Hospital in Nepal, and the University of California, San Francisco, who had culture-positive fungal ulcer and baseline visual acuity of 20/400 or worse were randomized to receive oral voriconazole vs placebo. Enrollment started May 24, 2010, and the last patient study visit was November 23, 2015. All patients received topical voriconazole, 1%, and after the results of the Mycotic Ulcer Treatment Trial (MUTT) II became available, topical natamycin, 5%, was added for all patients. Data analysis was performed from September 2 to October 28, 2016.

**MAIN OUTCOMES AND MEASURES** The primary outcome of the trial was the rate of corneal perforation or the need for therapeutic penetrating keratoplasty. Secondary outcomes included rate of reepithelialization, best spectacle-corrected visual acuity, and infiltrate or scar size at 3 months.

**RESULTS** Of the 240 study participants, 72 (30.4%) were culture positive for *Fusarium* species (41 [56.9%] male and 31 [43.1%] female; median [interquartile range] age, 50 [45-57] years). Of these, 33 (45.8%) were randomized to oral voriconazole and 39 (54.2%) to placebo. *Fusarium* ulcers randomized to oral voriconazole had a 0.43-fold decreased hazard of perforation or therapeutic penetrating keratoplasty compared with placebo after controlling for baseline infiltrate depth (95% CI, 0.22-fold to 0.84-fold; *P* = .01). Multiple linear regression revealed a 1.89-mm decreased infiltrate and/or scar size at 3 weeks (95% CI, −2.69 to −1.09 mm; *P* < .001) and a 0.83-mm decreased infiltrate and/or scar size at 3 months after correcting for baseline values (95% CI, −1.33 to −0.32 mm; *P* = .001) in eyes randomized to oral voriconazole vs placebo. Eyes treated with oral voriconazole also had a mean 0.29 decreased logMAR (improved) (Snellen equivalent 20/40) visual acuity at 3 months after controlling for baseline visual acuity, although this finding was not statistically significant (95% CI, −0.57 to 0.002; *P* = .052).

**CONCLUSIONS AND RELEVANCE** Although MUTT II could not find a benefit for all corneal ulcers, *Fusarium* keratitis may benefit from the addition of oral voriconazole to topical natamycin, and physicians should consider prescribing oral voriconazole in these cases.

**TRIALREGISTRATION** clinicaltrials.gov Identifier: NCT00996736


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Fusarium species are ubiquitous filamentous fungi that are the most common organism implicated in fungal keratitis, particularly in tropical regions. In 2006, an epidemic of Fusarium keratitis was reported in contact lens wearers who were using Bausch & Lomb ReNU with MoistureLoc (Bausch & Lomb) contact lens solution in the United States and Asia.2-5 Many of these patients had severe vision loss, and more than one-third ultimately required corneal transplant for visual rehabilitation. Fusarium has also been recognized as an emerging systemic pathogen in individuals with immunosuppression that is associated with a high mortality rate and little evidence to guide therapy.2,7

The Mycotic Ulcer Treatment Trial (MUTT) I found that topical natamycin was superior to topical voriconazole for the treatment of filamentary keratitis.8 Fusarium species represented approximately 40% (N = 128) of the ulcers in the study, and these patients had 4 lines of visual acuity improvement when treated with natamycin compared with voriconazole. One reason for this may be that intermittent administration of topical voriconazole produces concentration peaks and troughs that result in intervals of subtherapeutic drug levels. Oral medications provide more steady state drug levels in aqueous samples.9 MUTT II, which investigated the benefit of adjunct oral voriconazole in the treatment of filamentous fungal ulcers, failed to show a benefit of oral voriconazole for all filamentous fungi.10 However, a previous study11 found that the response to topical voriconazole appeared to vary by etiologic organism. In this study, we investigate the effect of adjunct oral voriconazole on clinical outcomes specifically for patients with Fusarium corneal ulcers.

Methods

The methods for MUTT II have been outlined in detail in a previous publication.10 In brief, patients who presented with a culture-positive filamentous fungal corneal ulcer and a visual acuity less than or equal to 20/400 (logMAR 1.3) were randomized to oral voriconazole vs placebo. All patients received topical voriconazole, 1%, and after the results of MUTT I became available, topical natamycin, 5%, was added for all patients. Enrollment started May 24, 2010, and the last patient study visit was November 23, 2015. Enrollment centers included hospitals in the Aravind Eye Care System (Madurai, Pondicherry, Tirunelveli, or Coimbatore, India), the Lumbini Eye Hospital and the Bharatpur Eye Hospital in Nepal, and the University of California, San Francisco. Exclusion criteria included coinfection with bacteria, Acanthamoeba, or herpes simplex virus; impending perforation; age younger than 16 years; poor visual acuity in the other eye (<20/200); weight less than 40 kg; or known liver disease or pregnancy. Written informed consent was obtained from all participants, and the trial conformed to the Declaration of Helsinki. All data were deidentified. The Data and Safety Monitoring Committee performed ongoing reviews for safety, data quality, and ethical conduct throughout the length of the trial. Institutional review board approval was obtained from the University of California, San Francisco; the Aravind Eye Care System; the Dartmouth-Hitchcock Medical Center Committee for the Protection of Human Subjects; and Nepal Netra Jyoti Sangh (see the full trial protocol in the Supplement).

The primary outcome of the trial was rate of perforation or the need for therapeutic penetrating keratoplasty (TPK). Secondary outcomes included visual acuity, scar size at 3 weeks and 3 months, and the rate of reepithelialization. Determination of the effect of oral voriconazole on outcomes for Fusarium ulcers was a prespecified secondary analysis in MUTT II. The chosen sample size for our study was based on the primary outcome, and we estimated that 240 study participants would provide 80% power to detect a 15% difference in 3-month perforation rate with a 2-tailed α = .05 and approximately 15% loss to follow-up.

For the primary outcome of this study, a Cox proportional hazards regression model was used to evaluate the effect of voriconazole on the rate of corneal perforation or the need for TPK in the prespecified Fusarium subgroup. A mixed linear regression model was used to assess best spectacle-corrected visual acuity (BSCVA) at 3 weeks and 3 months, controlling for baseline BSCVA and treating site as fixed effects. After TPK, we used the last observation carried forward before TPK or logMAR 1.7 (Snellen equivalent <20/800), whichever was worse. A sensitivity analysis using actual measured BSCVA after TPK was also performed. The 3-week and 3-month infiltrate and/or scar size was also compared with a mixed linear regression model that controlled for baseline values and treating site as fixed effects. Time to reepithelialization was analyzed using a Cox proportional hazards regression model, controlling for baseline epithelial defect size. Baseline characteristics between the 2 arms were compared using the Fisher exact test for categorial variables and the Wilcoxon rank sum test for continuous variables. All analyses were conducted using STATA statistical software, version 13 (StataCorp). Data analysis was performed from September 2 to October 28, 2016.

Results

Of the 240 study participants, 72 (30.4%) were culture positive for Fusarium species (41 [56.9%] male and 31 [43.1%] female; median [interquartile range (IQR)] age, 50 [45-57]...
General poor ocular health included limbus, endophthalmitis, vitritis, Hansen disease, aphakic bullous keratopathy, monocular, sclera, cataract, glaucoma, neurotrophic ulcer, and uveitis. General poor health included diabetes and hypertension.

years). Of these, 33 (45.8%) were randomized to oral voriconazole and 39 (54.2%) to placebo (Figure 1). All study participants were of Southeast Asian descent. Median baseline visual acuity was logMAR 1.70 (IQR, 1.44-1.80) (Snellen equivalent <20/800), and median baseline infiltrate size was 5.45 mm (IQR, 4.60-6.93 mm). There were no major differences in baseline characteristics between groups (Table 1).

Three-month follow-up was available for 56 (77.8%) of the 72 patients. A total of 19 perforations (26.4%) were found among Fusarium ulcers, with 12 (30.8%) of 33 occurring in the placebo arm and 7 (17.9%) of 39 in the oral voriconazole arm. Of the perforations, 6 (31.6%) were managed conservatively, and 13 (68.4%) progressed to a TPK. An additional 23 Fusarium ulcers (31.9%), including 14 (42.4%) of 33 in the placebo arm and 9 (23.1%) of 39 in the oral voriconazole arm, had risk of involvement of the limbus or increasing infiltrate despite current best standard medical therapy and progressed to a TPK at the discretion of the masked treating ophthalmologist.

Fusarium species had a 0.43-fold decreased hazard of perforation or TPK with oral voriconazole vs placebo after controlling for baseline infiltrate depth, and this difference was statistically significant (95% CI, 0.22-fold to 0.84-fold; P = .01). Figure 2 shows the Kaplan-Meier curve for the rate of perforation or TPK in Fusarium ulcers by treatment arm. Sensitivity analysis that controlled for the addition of topical natamycin later in the trial did not appreciably change the analysis.

Table 2 outlines the secondary outcomes of the study. Median 3-month logMAR visual acuity was 1.70 (IQR, 1.30-1.80) (Snellen equivalent <20/300) in the placebo group and 1.30 (IQR, 0.54-1.80) (Snellen equivalent 20/400) in those randomized to receive oral voriconazole. When we assigned a visual acuity value of logMAR 1.70 for those with TPK or last observation carried forward, whichever was worse, Fusarium ulcers had a mean 0.12 decreased logMAR visual acuity (improved) (Snellen equivalent 20/250) at 3 weeks (95% CI, −0.34 to 0.10; P = .29) and a 0.29 decreased logMAR (improved) (Snellen equivalent 20/400) visual acuity at 3 months in those treated with oral voriconazole after controlling for baseline visual acuity, although this finding was not statistically significant (95% CI, −0.57 to 0.002; P = .052). A sensitivity analysis using measured BSCVA at 3 months despite TPK did not substantially change the results of the analysis.

In eyes randomized to oral voriconazole vs placebo, multiple linear regression revealed a 1.89-mm decreased infiltrate and/or scar size at 3 weeks (95% CI, −2.69 to −1.09 mm; P < .001) and 0.83-mm decreased infiltrate and/or scar size at 3 months after correcting for baseline values (95% CI, −1.33 to −0.32 mm; P = .001). There was no statistically significant difference in rate of reepithelialization between groups after controlling for baseline epithelial defect size (hazard ratio, 1.85; 95% CI, 0.56-6.06; P = .31).

### Discussion

Because Fusarium are among the most common species associated with fungal keratitis worldwide, it is important to identify specific therapeutic strategies for this group that might improve treatment outcomes. In this study, we found a decreased rate of perforation and/or need for TPK and a decreased scar size among Fusarium ulcers treated with oral voriconazole in addition to topical antifungals. There also appeared to be improved visual acuity and faster reepithelialization, although these findings were not statistically significant.

Although MUTTI II did not find a benefit to the addition of oral voriconazole, MUTTI I already revealed that response to voriconazole can be dependent on the organism subtype. In a prior in vitro study of fungal samples from corneal ulcers, all isolates were susceptible to voriconazole. However, Fusarium species had the highest minimum inhibitory concentration (MIC), a measure of fungal drug resistance. Although topical therapy can deliver a high concentration of antimicrobial to the site of infection, limitations include ocular penetration and achievement of steady state therapeutic drug concentration at the site of infection. In one study, aqueous samples after topical administration of voriconazole, 1%, every 2 hours had a voriconazole concentration of approximately 6 μg/mL. This finding is noteworthy because in vitro...
studies report the MIC required to inhibit the growth of organisms (MIC90) of Fusarium to be 4 to 16 μg/mL compared with Aspergillus and other filamentous fungi, which have an MIC90 of approximately 2 μg/mL. Oral voriconazole has excellent ocular penetration and ability to provide more consistent drug levels. One study that compared aqueous samples after topical and oral voriconazole found that topical administration of voriconazole resulted in highly variable aqueous concentrations with troughs well below the MIC90 for most fungi, whereas oral voriconazole had a therapeutic drug level that remained relatively constant. Although topical therapy alone may be sufficient treatment for fungi with lower voriconazole MICs, the high MIC90 of Fusarium species to voriconazole may explain why the addition of oral voriconazole was more effective than a topical agent alone.

Another possible explanation for our finding is a synergistic or additive association between natamycin and voriconazole for Fusarium species. One in vitro study found that the combination was synergistic against 70% of Fusarium strains.
Table 2. Secondary Outcomes in Fusarium Ulcers Receiving Oral Voriconazole vs Placebo

<table>
<thead>
<tr>
<th>Covariate Result (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1: Multiple Linear Regression Predicting 3-mo BSCVA, Median logMAR (IQR) [Snellen Equivalent]</strong></td>
<td></td>
</tr>
<tr>
<td>No. 56</td>
<td></td>
</tr>
<tr>
<td>Oral voriconazole (vs placebo)</td>
<td>-0.29 (-0.57 to 0.002) [-20/3]</td>
</tr>
<tr>
<td>Baseline BSCVA</td>
<td>0.48 (0.05 to 0.91)</td>
</tr>
<tr>
<td><strong>Model 2: Multiple Linear Regression Predicting 3-mo Infiltrate or Scar, Median (Range), mm</strong></td>
<td></td>
</tr>
<tr>
<td>No. 54</td>
<td></td>
</tr>
<tr>
<td>Oral voriconazole (vs placebo)</td>
<td>-0.83 (-1.33 to -0.32)</td>
</tr>
<tr>
<td>Baseline infiltrate/Scar</td>
<td>0.60 (0.41 to 0.78)</td>
</tr>
<tr>
<td><strong>Model 3: Cox Proportional Hazards Regression Model Predicting Time to Reepithelialization, HR (95% CI)</strong></td>
<td></td>
</tr>
<tr>
<td>No. 71</td>
<td></td>
</tr>
<tr>
<td>Oral voriconazole (vs placebo)</td>
<td>1.85 (0.56 to 6.06)</td>
</tr>
<tr>
<td>Baseline epithelial size</td>
<td>0.40 (0.27 to 0.58)</td>
</tr>
</tbody>
</table>

Abbreviations: BSCVA, best spectacle-corrected visual acuity; HR, hazard ratio; IQR, interquartile range.

* Coefficient for multiple linear regression and HR for Cox proportional hazards regression model.

Conclusions

*Fusarium* corneal ulcers may benefit from the addition of oral voriconazole to topical natamycin. Physicians should consider prescribing oral voriconazole for severe corneal ulcers if the infectious organism is *Fusarium* species.

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Challenges in the Management of Fungal Keratitis

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Fungal keratitis is a challenging ophthalmologic condition that requires a high level of suspicion and aggressive treatment to prevent untoward outcomes. Identifying this condition, in turn, necessitates an understanding of the regional demographic features of infectious keratitis. Fungal keratitis is more commonly encountered in the tropical and subtropical parts of the world, such as in south India, where fungi cause up to 47% of keratitis cases and where filamentous fungi, such as *Fusarium* and *Aspergillus*, predominate. However, fungal keratitis also occurs in the more temperate areas of the world but more often caused by yeasts, such as *Candida*. However, exceptions occur, such as with the *Fusarium* outbreak that was associated with contact lens wear.

Although there continues to be controversy with regard to the best antifungal treatment for various types of fungal keratitis, an understanding of the suspected causative organism when initiating treatment is still essential.

*Natamycin, 5%,* is the only US Food and Drug Administration-approved topical ophthalmic antifungal medication, and it has theoretical benefits in treating all types of fungal infections. However, extemporaneously compounded topical voriconazole and amphotericin B are also frequently used by cornea specialists for treating fungal keratitis. Because of a lack of data to support the superiority of one drug, the Mycotic Ulcer Treatment Trial (MUTT) I was undertaken, which found that topical natamycin is superior to topical voriconazole for the treatment of filamentous fungal corneal ulcers.

MUTT II was a randomized clinical trial performed in India and Nepal that evaluated the addition of oral voriconazole vs placebo to topical antifungal therapy for fungal keratitis. This study found that adding oral voriconazole to topical antifungal agents did not improve outcomes in the treatment of severe filamentous fungal ulcers, most of which were caused by *Fusarium* or *Aspergillus*.

In the present study, the authors of MUTT II performed a prespecified subgroup analysis of the MUTT II data looking at the 72 ulcers (of the total 240 from MUTT II) that were culture positive for *Fusarium*. In this subgroup, the data suggest that *Fusarium* corneal ulcers may benefit from the addition of oral voriconazole to topical antifungals.

This trial was well conducted. Despite a change in the topical medication regimen during the enrollment period (the MUTT I results were released during the enrollment period revealing superiority of natamycin over topical voriconazole), resulting in the addition of natamycin to topical voriconazole for the baseline treatment to which oral voriconazole or placebo was randomized, robust statistical measures affirmed the results. However, although not statistically significant, the finding that 6 individuals in the oral placebo group were using systemic antifungals at presentation compared with only 2 in the oral voriconazole group is deserving of mention. A prior subgroup analysis of MUTT I suggested that pretreatment with appropriate antifungal agents (including oral azoles) could be a risk factor for worse outcomes. This is likely because of initial ulcer severity and/or treatment failure. It is thus possible that these cases for which pretreatment with oral antifungals was given may