Published in final edited form as:
Br J Ophthalmol. 2012 November ; 96(11): . doi:10.1136/bjophthalmol-2012-301825.

Natamycin and voriconazole in *Fusarium* and *Aspergillus* keratitis: subgroup analysis of a randomised controlled trial

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INTRODUCTION

Fusarium and *Aspergillus* species are aggressive corneal pathogens, and even with proper treatment, can lead to poor outcomes.[1] Voriconazole is effective in vitro against *Aspergillus* species, but may not perform as well against *Fusarium* species.[2] We undertook a clinical trial comparing topical voriconazole versus topical natamycin, with the overall results presented previously.[3] Here, we perform a prespecified subgroup analyses of treatment within *Fusarium* cases, and separately, within *Aspergillus* cases, assessing the efficacy of voriconazole and natamycin.

METHODS

Complete methods of the clinical trial have been reported elsewhere.[3] In brief, eligible patients had a KOH-positive fungal smear with filamentous fungal elements, and were randomised to receive either topical voriconazole 1% (Pfizer, New York, NY, USA) or natamycin 5% (Alcon, FtWorth, Texas, USA), and to repeat scraping or no rescraping. The

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Competing interests None.

Ethics approval University of California, San Francisco Committee on Human Research; Aravind Eye Hospital Institutional Review Board.

Provenance and peer review Not commissioned; internally peer reviewed.

primary outcome for the trial was best spectacle-corrected visual acuity (BSCVA) at 3 months from enrolment. Secondary outcomes included corneal perforation and/or therapeutic penetration keratoplasty (TPK) by treatment arm. Fungal cultures were performed for all patients enrolled in the trial. Fungal identification was performed using gross and microscopic characteristics. Ethical approval was obtained from the University of California, San Francisco and the Aravind Eye Care System.

Analyses were performed in the subset of patients who were diagnosed with *Fusarium* or *Aspergillus* keratitis. Wilcoxon rank sum and Fisher's exact tests were used to analyse baseline characteristics. Linear regression was used to analyse the effect of voriconazole (vs natamycin) on BSCVA and scar size, controlling for baseline BSCVA and infiltrate size, respectively. Corneal perforation between the treatment groups was assessed using logistic regression, controlling for baseline infiltrate depth, using Firth's correction. Analyses were performed in Stata V.10.0 (StataCorp, College Station, Texas, USA).

RESULTS

Of 120 smear-positive cases of fungal keratitis enrolled in the trial, 101 had positive growth on culture (84%). Forty-four were identified as *Fusarium* species (44%): 21 were randomised to natamycin (48%) and 23 to voriconazole (52%). Nineteen isolates were identified as *Aspergillus* species, two of which were mixed infections, so 17 (17%) were included in this analysis (11 (58%) *A flavus*, 5 (26%) *A fumigatus* and 1 (5%) *A terreus*); 10 were randomised to natamycin (59%) and 7 to voriconazole (41%). At baseline, median infiltrate/scar size in *Fusarium* cases was 3.2 mm (IQR 2.2–5.1) in the natamycin arm and 3.7 mm (IQR 2.7–4.3) in the voriconazole arm (p=0.68). Median infiltrate/scar size in *Aspergillus* cases was 4.1 mm (IQR 3.4–6.0) in the natamycin arm, and 4.4 mm (IQR 2.1–5.5) in the voriconazole arm (p=0.44). The majority of patients in each arm in both *Fusarium* and *Aspergillus* cases had an infiltrate depth of >0–33% at baseline (for Fusarium, 11 of 21, 52%, in the natamycin arm, and 16 of 23, 70%, in the voriconazole arm, p = 0.60; for Aspergillus, 6 of 10, 60%, in the natamycin arm, and 4 of 7, 57% in the voriconazole arm, p = 1.00).

In *Fusarium* cases, there was no difference in 3-month BSCVA with voriconazole versus natamycin (0.11 logMAR, 95% CI −0.24 to 0.46, p = 0.54). Voriconazole was associated with an increase in perforation in *Fusarium* cases (OR 33.4, 95% CI 1.16 to 962.9, p = 0.041, table 1). Of seven perforations total in *Fusarium* cases, six were in the voriconazole arm and one in the natamycin arm. Six TPKs were performed, all of which were in cases that had perforated, five in the voriconazole arm and one in the natamycin arm. In *Aspergillus* cases, there was no difference in 3-month BSCVA with voriconazole versus natamycin (−0.21 logMAR, 95% CI −0.71 to 0.29, p = 0.38) or perforation (OR 0.09, 95% CI 0.0002 to 40.6, p = 0.44, table 1). Of four perforations, three were in the natamycin arm and one was in the voriconazole arm. Of these, there were two TPKs in the natamycin arm, and one in the voriconazole arm. There was one additional TPK in a case in the natamycin arm that had not perforated. There was no difference in perforation between the cases randomised to rescraping or no rescraping in either the *Fusarium* species or *Aspergillus* species subgroups.

COMMENT

We found no difference in 3-month BSCVA or scar size between voriconazole- and natamycin-treated patients in *Fusarium* or *Aspergillus* keratitis. However, voriconazole-treated *Fusarium* cases were more likely to perforate than natamycin-treated patients. There are conflicting reports about the efficacy of voriconazole against *Fusarium* species in vitro,

as well as reports of treatment failures with voriconazole despite a relatively low MIC_{90}.[245] Of the five perforations and/or TPKs in *Aspergillus*, four were in natamycin-treated cases. Overall in the trial, there was no difference between voriconazole and natamycin in 3-month BSCVA or in proportion of cases perforating.[3] Even when prespecified, subgroup analyses need to be treated with caution. These numbers are small, and further research is warranted on differential effect of voriconazole and natamycin in *Fusarium* and *Aspergillus* keratitis.

Acknowledgments

Funding Alcon Inc donated natamycin, and Pfizer Inc donated voriconazole for the study. None of the authors have any financial disclosures related to this manuscript. Funding for this research was from That Man May See and the South Asia Research Fund. The Department of Ophthalmology at UCSF is supported by a core grant from the National Eye Institute, EY02162. Dr Acharya is supported by a National Eye Institute K23EY017897 grant and a Research to Prevent Blindness Career Development Award. Dr Lietman is supported by a National Eye Institute grant U10-EY015114 and a Research to Prevent Blindness award. Dr Porco is supported by That Man May See Foundation at UCSF. The sponsors did not have role in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript.

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Table 1

Perforation in *Fusarium* and *Aspergillus* keratitis patients

	***Fusarium* species (n=44)**		***Aspergillus* species (n=17)**	
Covariate	**OR (95% CI)***	**p Value**	**OR (95% CI)***	**p Value**
Voriconazole (vs natamycin)	3.51 (0.15 to 6.87)	0.041	0.09 (0.00 to 40.6)	0.44
Rescraping (vs not rescraping)	0.19 (−1.87 to 2.24)	0.86	0.34 (0.00 to 50.0)	0.67
Depth at enrolment	2.59 (0.57 to 4.61)	0.012	5.8 (0.45 to 75.2)	0.18

* Logistic regression predicting perforation with voriconazole (vs natamycin), rescraping (vs not rescraping), and infiltrate depth at baseline as covariates, using a Firth correction.