JOURNAL CLUB

The Mycotic Ulcer Treatment Trial

A Randomized Trial Comparing Natamycin vs Voriconazole

N. Venkatesh Prajna, MD; Tiruvengada Krishnan, MD; Jeena Mascarenhas, MD; Revathi Rajaraman, MD; Lalitha Prajna, MD; Muthiah Srinivasan, MD; Anita Raghavan, MD; Catherine E. Oldenburg, MPH; Kathryn J. Ray, MA; Michael E. Zegans, MD; Stephen D. McLeod, MD; Travis C. Porco, PhD, MPH; Nisha R. Acharya, MD, MS; Thomas M. Lietman, MD; for the Mycotic Ulcer Treatment Trial Group

Objective: To compare topical natamycin vs voriconazole in the treatment of filamentous fungal keratitis.

Methods: This phase 3, double-masked, multicenter trial was designed to randomize 368 patients to voriconazole (1%) or natamycin (5%), applied topically every hour while awake until reepithelialization, then 4 times daily for at least 3 weeks. Eligibility included smear-positive filamentous fungal ulcer and visual acuity of 20/40 to 20/400.

Main Outcome Measures: The primary outcome was best spectacle-corrected visual acuity at 3 months; secondary outcomes included corneal perforation and/or therapeutic penetrating keratoplasty.

Results: A total of 940 patients were screened and 323 were enrolled. Causative organisms included *Fusarium* (128 patients [40%]), *Aspergillus* (54 patients [17%]), and other filamentous fungi (141 patients [43%]). Natamycin-treated cases had significantly better 3-month best spectacle-corrected visual acuity than voriconazole-treated cases (regression coefficient = −0.18 logMAR; 95% CI, −0.30 to −0.05; $P = .006$). Natamycin-treated cases were less likely to have perforation or require therapeutic penetrating keratoplasty (odds ratio = 0.42; 95% CI, 0.22 to 0.80; $P = .009$). *Fusarium* cases fared better with natamycin than with voriconazole (regression coefficient = −0.41 logMAR; 95% CI, −0.61 to −0.20; $P < .001$; odds ratio for perforation = 0.06; 95% CI, 0.01 to 0.28; $P < .001$), while non-*Fusarium* cases fared similarly (regression coefficient = −0.02 logMAR; 95% CI, −0.17 to 0.13; $P = .81$; odds ratio for perforation = 1.08; 95% CI, 0.48 to 2.43; $P = .86$).

Conclusions: Natamycin treatment was associated with significantly better clinical and microbiological outcomes than voriconazole treatment for smear-positive filamentous fungal keratitis, with much of the difference attributable to improved results in *Fusarium* cases.

Application to Clinical Practice: Voriconazole should not be used as monotherapy in filamentous keratitis.

Trial Registration: clinicaltrials.gov Identifier: NCT00996736

JAMA Ophthalmol. 2013;131(4):422-429.
Published online December 10, 2012.
doi:10.1001/jamaophthalmol.2013.1497

Author Affiliations are listed at the end of this article.
Group Information: The Mycotic Ulcer Treatment Trial Group members are listed at the end of this article.

INFECTIOUS KERATITIS IS A LEADING cause of monocular vision loss worldwide, with approximately 2 million new cases each year.[1] Fungal keratitis is endemic in tropical regions, accounting for as many as half of all corneal ulcers.[2] While the incidence of fungal keratitis is typically much lower in temperate regions, a recent epidemic included parts of Asia and North America.[3-7]

Journal Club slides available at www.jamaophth.com

Fungal corneal ulcers can be more difficult to treat than bacterial corneal ulcers, with worse outcomes.[8] Natamycin is the only topical antifungal approved by the US Food and Drug Administration for topical ophthalmic use. A recent survey revealed that 80% of corneal specialists believed that existing treatments for fungal ulcers were only moderately effective and that, if available, voriconazole would be the preferred treatment of choice for filamentous fungal keratitis.[9] Most isolates from fungal keratitis have good in vitro susceptibility to newer azoles, including voriconazole.[10,11] A previous small randomized controlled trial found a nonsignificant benefit of voriconazole in the subgroup of patients who initially had visual acuity of 20/40 to 20/400.[12] Herein, we report the results of a larger trial designed to definitively determine whether topical natamycin or voriconazole results in better outcomes in fungal keratitis.

METHODS

TRIAL DESIGN

The Mycotic Ulcer Topical Treatment Trial I (MUTT I) was a National Eye Institute–supported, randomized, active comparator–controlled, double-masked, multicenter clinical trial comparing outcomes in patients with fungal corneal ulcers receiving topical natamycin, 5% (Natacyn; preserved with benzalkonium chloride, 0.01%) and topical voriconazole, 1% (Vfend IV; reconstituted in sterile water for injection with benzalkonium chloride, 0.01%, by Aurolab). Double-masking was achieved through Aurolab packaging both the natamycin suspension and the voriconazole solution in identical opaque containers (3 mL/container) and ophthalmic assistants carefully irrigating each patient's eye prior to examination. The primary outcome was best spectacle-corrected visual acuity (BSCVA) 3 months from enrollment. Secondary outcomes included BSCVA at 3 weeks, infiltrate or scar size at 3 weeks and 3 months, time to reepithelialization, microbiological cure at 6 days (±1 day), and corneal perforation and/or therapeutic penetrating keratoplasty (TPK). Patients, physicians, and investigators were all masked to treatment until the conclusion of the trial.

STUDY PARTICIPANTS

Eligible patients had a smear-positive fungal corneal ulcer and baseline visual acuity of 20/40 (0.3 logMAR) to 20/400 (1.3 logMAR) (**Table 1**). Reasons for exclusion included impending perforation, evidence of bacterial, *Acanthamoeba*, or herpetic keratitis, being younger than 16 years, and bilateral ulcers or visual acuity worse than 20/200 (1.0 logMAR) in the nonaffected eye. Masked assignment to the treatment intervention was performed after determination of eligibility and consent to participate. Enrollment centers included the Aravind Eye Care System in India (Madurai, Pondicherry, and Coimbatore) and the Francis I. Proctor Foundation, University of California, San Francisco.

Table 1. Inclusion and Exclusion Criteria for the Mycotic Ulcer Topical Treatment Trial I

Criteria
Inclusion, all must be met
Presence of a corneal ulcer at initial visit
Evidence of filamentous fungus on smear, potassium hydroxide wet mount, Giemsa staining, or Gram staining
Basic understanding of the study including commitment to return for follow-up visits
Willingness to be treated as an inpatient or to return every 3 d (±1 d) until reepithelialization and every 1 wk (±2 d) to receive fresh medication for 3 wk
Appropriate consent
Visual acuity between 6/12 (20/40) and 6/120 (20/400), inclusive
Exclusion, any exclude
Impending perforation
Evidence of bacteria on Gram staining at time of enrollment
Evidence of *Acanthamoeba* by staining
Evidence of herpetic keratitis by history or examination
Corneal scar not easily distinguishable from current ulcer
Age <16 y, before 16th birthday
Bilateral ulcers
Previous keratoplasty in affected eye
Pregnancy, by history or urine test, or breastfeeding, by history
Visual acuity <6/60 (<20/200) in fellow eye
Known allergy to study medications
No light perception in affected eye
Not willing to participate

INTERVENTION

Patients were randomized to receive topical natamycin or voriconazole after determination of eligibility. Dosing schedules were identical in the arms and consisted of 1 drop applied to the affected eye every 1 hour while awake for 1 week, then every 2 hours while awake until 3 weeks from enrollment. Further continuation of the masked medication was then at the discretion of the physician. All antifungal medications were kept refrigerated or in a dark, cool place. Topical medications were switched with fresh bottles every 7 days (±2 days). For ethical reasons, physicians were allowed to add or change medications if deemed medically necessary.

MAIN OUTCOME MEASURES

Patients were assessed at enrollment, every 3 days (±1 day) until reepithelialization, and additionally at 3 weeks and 3 months from enrollment. The BSCVA was measured at enrollment, 3 weeks, and 3 months by masked refractionists certified for the study. The BSCVA protocol was adapted from the Age-Related Eye Disease Study using Early Treatment Diabetic Retinopathy Study tumbling "E" charts (charts 2305 and 2305A; PrecisionVision) at 4 m, using a protocol identical to that used in the Steroids for Corneal Ulcers Trial, with low-vision testing at 0.5 m.[13,14]

A calibrated slitlamp biomicroscope was used to assess the size of the infiltrate or scar, epithelial defect, depth, hypopyon, and ocular adverse events at enrollment, every 3 days (±1 day), 3 weeks from enrollment, and 3 months from enrollment. Infiltrate or scar size and epithelial defect size were measured in a protocol identical to the Steroids for Corneal Ulcers Trial[14] by measuring the longest dimension and the longest perpendicular, a protocol adapted from the Herpetic Eye Disease Study.[15] As in the Steroids for Corneal Ulcers Trial, reepithelialization was defined as the absence of an epithelial defect with the administration of fluorescein. Depth was assessed in 3 categories: more than 0% to 33%; more than 33% to 67%; and more than 67% to 100%. All grading ophthalmologists were certified for the study and masked to treatment assignment.

MICROBIOLOGICAL METHODS

Corneal scrapings were obtained after determination of initial visual acuity and slitlamp examination and after administration of topical anesthetic (tetracaine hydrochloride, 0.5%, or lidocaine hydrochloride, 4%). A flame-sterilized Kimura spatula was used to obtain a scrape from the leading edge and base of the corneal ulcer. Two scrapings were smeared directly on separate glass slides for Gram staining and potassium hydroxide wet mount, and 3 further scrapings were taken and directly inoculated onto sheep's-blood agar, chocolate agar, and potato-dextrose agar or Sabouraud agar for bacterial and fungal cultures. Fungal smears were considered positive when fungal elements were seen under low-power magnification and reduced light. Fungal cultures were considered positive with growth on any 2 media or moderate to heavy growth on 1 medium. Repeated cultures were performed at 6 days (±1 day) using the same protocol.

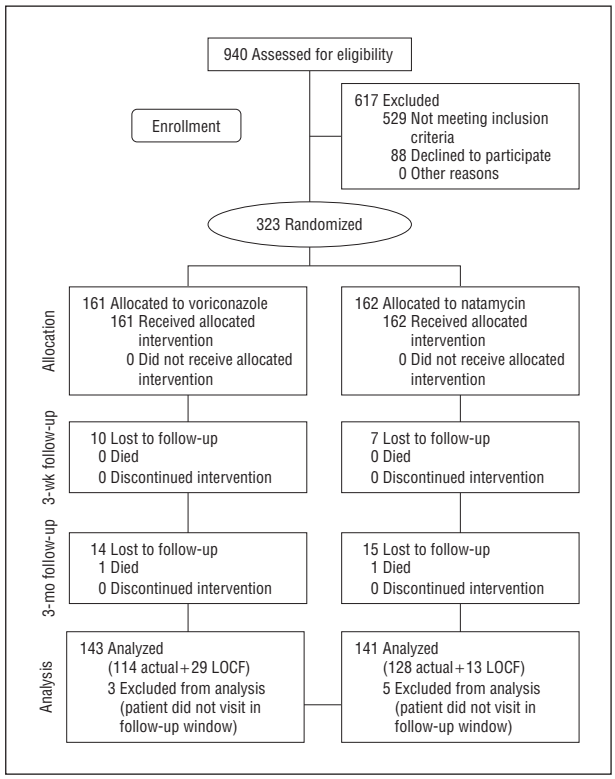

Figure 1. The CONSORT flow diagram for the Mycotic Ulcer Topical Treatment Trial I. LOCF indicates last observation carried forward as described in "Methods."

STATISTICAL ANALYSIS

A noninferiority threshold and a 2-sided confidence interval were prespecified to allow declaration of noninferiority of voriconazole and/or superiority of either drug. A simulation-based sample size of 368 patients (184 per arm) was fixed prior to enrollment and estimated to provide 80% power to detect a 0.15-logMAR difference in BSCVA 3 months after enrollment between the 2 arms, assuming 0.46 SD for 3-month BSCVA, a type I error rate of .05, a 2-tailed test, and a 15% dropout rate. A random allocation sequence was generated (T.C.P. and K.J.R.) for patients by center in random block sizes of 4, 6, and 8.

Baseline characteristics between the 2 arms were compared using Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Multiple linear regression was the primary prespecified analysis, predicting 3-month BSCVA with treatment arm and baseline BSCVA as covariates. Noninferiority was prespecified as the lower bound of the 1-sided 97.5% confidence limit of the regression coefficient exceeding −1.5 Snellen lines (−0.15 logMAR units). Note that the prespecified 2-sided confidence interval was included specifically to allow superiority comparisons. The geometric mean of the longest diameter and the longest perpendicular was used to assess infiltrate or scar size and epithelial defect size. We fit a linear model for the infiltrate or scar size using treatment arm and infiltrate or scar size at enrollment as covariates. Time to reepithelialization was analyzed using a Cox proportional hazards model with treatment arm and epithelial defect size at enrollment as covariates. The proportion of adverse events in the 2 arms was compared with Fisher exact test. A logistic regression model with covariates for treatment arm and baseline infiltrate depth was used to assess the odds of corneal perforation and/or TPK. Subgroup analysis used the same methods as stated for the primary analysis.

After TPK, we arbitrarily assigned a 3-month logMAR of 1.7 or the 3-week value (if the TPK had not occurred), whichever was worse. For infiltrate or scar size and for epithelial defect size, we used the most recent value for each patient prior to the surgery. Sensitivity analyses for patients lost to follow-up were conducted using linear mixed-effects regression including all outcomes measured for each patient. All analyses were conducted using R version 2.12 software for Macintosh (R Foundation for Statistical Computing).

INTERIM MONITORING

The Data Safety and Monitoring Committee performed 3 interim reviews for safety, data quality, and trial conduct. Efficacy was assessed using the Lan-DeMets flexible α spending function to preserve the overall type I error rate.

ETHICAL APPROVAL

Ethical approval was obtained from the Aravind Eye Care System Institutional Review Board, the University of California, San Francisco Committee on Human Research, and the Dartmouth-Hitchcock Medical Center Committee for the Protection of Human Subjects. Informed consent was obtained from all participants, and the trial conformed to the Declaration of Helsinki.

RESULTS

Between April 3, 2010, and December 31, 2011, 323 patients were enrolled at the Aravind Eye Care Hospitals in Madurai (164 patients), Pondicherry (86 patients), and Coimbatore (73 patients) (**Figure 1**). The Data Safety and Monitoring Committee reviewed results from 323 patients on February 27, 2012. At that point, 34 perforations and/or TPKs had occurred among patients randomized to voriconazole and 18 had occurred among those randomized to natamycin ($P = .02$). The Data Safety and Monitoring Committee recommended suspension of recruitment, the trial executive committee endorsed this recommendation, and recruitment was stopped immediately. Natamycin was added to the treatment regimens for all patients currently enrolled. Thus, only patients enrolled on or before December 31, 2011, were included in the final primary analysis (323 patients).

A total of 940 patients were screened between April 1, 2010, and December 31, 2011, and 323 patients were randomly assigned to topical voriconazole (161 patients) or topical natamycin (162 patients) (Figure 1). The baseline demographic and clinical characteristics are displayed in **Table 2** and **Table 3**, respectively. The most commonly isolated organisms were *Fusarium* species (128 patients [40%]), followed by *Aspergillus* species (54 patients [17%]) (**Table 4**). The median duration of treatment was 31 days (interquartile range, 21-50 days) in the natamycin-treated arm and 39 days (interquartile range, 28-53 days) in the voriconazole-treated arm ($P = .006$).

At 3 weeks, the mean BSCVA among patients randomized to voriconazole was 1.1 lines poorer compared with those randomized to natamycin (regression coefficient = −0.11 logMAR; 95% CI, −0.21 to −0.01; $P = .03$).

Table 2. Baseline Demographic Characteristics

Characteristic	Voriconazole (n = 161)	Natamycin (n = 162)	Total (N = 323)	*P* Value[a]
Sex, No.				.58
Male	94	89	183	
Female	67	73	140	
Age, median (IQR), y	45 (38-55)	48 (39-58)	47 (38-56)	.23
Occupation, No.				.74
Agriculture	76	80	156	
Nonagriculture[b]	85	82	167	
Medication use at enrollment, No.[c]				
Topical ocular antifungals	67	81	148	.15
Other topical eyedrops[d]	130	144	274	.04
Systemic antifungals	5	6	11	.99
Other systemic	43	45	88	.90
Trauma or injury, No.				
Vegetative matter or wood	40	42	82	.90
Metal or other[e]	53	58	111	.64
Unknown object	5	9	14	.41
Contact lens	0	0	0	>.99

Abbreviation: IQR, interquartile range.
[a] The *P* value for age was calculated by Wilcoxon rank sum test; all other *P* values were calculated by Fisher exact test.
[b] Includes unemployed, retired, etc.
[c] Some patients were receiving more than 1 medication at enrollment.
[d] Includes topical antibiotics, dilating eyedrops, glaucoma medication, and lubricating eyedrops.
[e] Includes dust, finger, kerosene, cement, fingernail, chili powder, sand, cow's tail, and insect.

Table 3. Baseline Clinical Characteristics

Characteristic	Voriconazole (n = 161)	Natamycin (n = 162)	Total (N = 323)	*P* Value[a]
Visual acuity, median (IQR)				
logMAR	0.64 (0.38-0.86)	0.66 (0.38-0.92)	0.64 (0.38-0.89)	.65
Snellen	20/90 (20/50-20/140)	20/90 (20/50-20/160)	20/90 (20/50-20/160)	.65
Infiltrate or scar size, median (IQR), mm[b]	3.2 (2.7-4.0)	3.1 (2.5-4.0)	3.2 (2.5-4.0)	.45
Hypopyon, No.				.36
None	104	109	213	
<0.5 mm	33	24	57	
>0.5 mm	24	29	53	
% Of depth, No.				.60
>0 to 33	91	83	174	
>33 to 67	55	64	119	
>67 to 100	15	15	30	
Epithelial defect, median (IQR), mm	2.6 (1.6-3.5)	2.5 (1.7-3.3)	2.5 (1.7-3.4)	.66
Duration of symptoms, median (IQR), d	5 (3-0)	5 (3-9)	5 (3-10)	.58
Ocular surface disease, No.	2	1	3	.62
Dacryostenosis or dacryocystitis, No.	0	0	0	>.99
Preexisting corneal abnormalities, No.[c]	3	1	4	.37
Preexisting eyelid or eyelash abnormalities, No.[d]	2	2	4	>.99
Systemic disease, No.[e]	10	12	22	.83

Abbreviation: IQR, interquartile range.
[a] The count data were analyzed with Fisher exact test; the continuous data were analyzed with Wilcoxon rank sum test.
[b] Geometric mean of the longest diameter and longest perpendicular to that diameter in millimeters.
[c] Includes corneal degeneration, spheroidal degeneration, climactic droplet keratopathy, bullous keratopathy, epithelial hyperplasia, lattice dystrophy, Fuchs dystrophy, and old scar due to keratitis.
[d] Includes ectropion of the lower eyelid, Bell palsy, eyelid laxity, lagophthalmos, eyelid scars, and madarosis.
[e] Includes diabetes mellitus, asthma, Hansen disease, eczema, psoriasis, human immunodeficiency virus, ichthyosis, hypertension, and malnutrition.

The 3-week mean BSCVA was 0.49 logMAR (95% CI, 0.42 to 0.57) in the natamycin-treated arm and 0.60 logMAR (95% CI, 0.51 to 0.70) in the voriconazole-treated arm. At 3 months, correcting for baseline BSCVA in each arm, we estimate that patients randomized to receive voriconazole did 1.8 lines worse than those randomized to receive natamycin (regression coefficient = −0.18 logMAR; 95% CI, −0.30 to −0.05; *P* = .006) (**Table 5**). The mean BSCVA was 0.39 logMAR (95% CI, 0.30 to 0.48) in the natamycin-treated arm and 0.57 logMAR (95% CI, 0.46 to 0.68) in the voriconazole-treated arm. Subgroup analysis (**Figure 2**) revealed that the mean

Table 4. Microbiological Culture Results[a]

Organism	No. (%) Voriconazole (n = 161)	Natamycin (n = 162)	Total (N = 323)
Fusarium species	66 (41)	62 (39)	128
Aspergillus species	28 (17)	26 (16)	54
Aspergillus flavus	18 (11)	14 (9)	32
Aspergillus fumigatus	5 (3)	6 (4)	11
Aspergillus niger	0	2 (1)	2
Aspergillus terreus	0	3 (2)	3
Other *Aspergillus*	5 (3)	1 (1)	6
Alternaria species	0	3 (2)	3
Biopolaris species	1 (1)	3 (2)	4
Curvularia species	9 (6)	11 (6)	20
Exserohilum species	7 (4)	2 (1)	9
Lasiodiplodia species	1 (1)	3 (2)	4
Unidentified hyaline fungus	7 (4)	10 (6)	17
Unidentified dematiaceous fungus	7 (4)	8 (4)	15
Other fungus	1 (1)	1 (1)	2
Fungal culture negative	34 (21)	33 (21)	67

[a]Comparing species, $P = .60$ by Fisher exact test.

BSCVA for *Fusarium*-infected patients randomized to natamycin was 4.1 lines better than for such patients randomized to voriconazole (regression coefficient = −0.41 logMAR; 95% CI, −0.61 to −0.20; $P < .001$). We found no evidence of a difference in adjusted BSCVA between the 2 treatments in non-*Fusarium* cases (regression coefficient = −0.02 logMAR; 95% CI, −0.17 to 0.13; $P = .81$). Thirty-nine visual acuity measurements were unavailable at the 3-month follow-up; we found no evidence that loss to follow-up was associated with baseline visual acuity, treatment assignment, or infection with *Fusarium* species.

A higher fraction of individuals randomized to voriconazole tested culture positive at 6 days than individuals randomized to natamycin: 23 of 155 patients (15%) (95% CI, 10% to 21%) for natamycin vs 69 of 144 patients (48%) (95% CI, 40% to 56%; $P < .001$) for voriconazole. Subgroup analysis revealed the same pattern both in *Fusarium* cases (natamycin-treated cases positive after 6 days: 5 of 60 patients [8%]; 95% CI, 3% to 18%; voriconazole-treated cases positive after 6 days: 36 of 60 patients [60%]; 95% CI, 46% to 72%; $P < .001$) and in non-*Fusarium cases* (natamycin-treated cases positive after 6 days: 18 of 95 patients [19%]; 95% CI, 12% to 28%; voriconazole-treated cases positive after 6 days: 33 of 84 patients [39%]; 95% CI, 29% to 50%; $P = .03$). Assuming negative results for the 24 individuals for whom no culture was taken at 6 days gave similar results (data not shown).

There was no compelling evidence of a difference in time to reepithelialization by treatment after controlling for baseline epithelial defect size (right censoring 21 days from enrollment). Cox proportional hazards regression yielded a hazard ratio for reepithelialization that was 1.25-fold higher with natamycin (95% CI, 0.95 to 1.65; $P = .11$). Subgroup analysis found that *Fusarium* cases healed significantly more rapidly with natamycin (hazard ratio = 1.89; 95% CI, 1.21 to 2.93; $P = .005$) but that non-*Fusarium* cases did not (hazard ratio = 1.00; 95% CI, 0.70 to 1.42; $P > .99$). At 3 months, there was evidence of a difference in scar size between patients randomized to the 2 treatments (regression coefficient = 0.31 mm larger for patients receiving voriconazole; 95% CI −0.002 to 0.62 mm; $P = .05$), adjusting for baseline infiltrate size. *Fusarium* cases had significantly smaller scars at 3 months when treated with natamycin (regression coefficient = −1.02 mm; 95% CI, −1.46 to −0.58 mm; $P < .001$), whereas we found no evidence of larger scars at 3 months for non-*Fusarium* cases (regression coefficient = −0.17 mm; 95% CI, −0.59 to 0.25 mm; $P = .42$).

Thirty-four patients randomized to receive voriconazole had a perforation and/or required a TPK, compared with 18 patients randomized to receive natamycin. In a logistic regression model, patients with ulcers randomized to natamycin were less likely to undergo perforation or transplantation (odds ratio = 0.42; 95% CI, 0.22 to 0.80; $P = .009$). In the *Fusarium* cases, the odds ratio for perforation was 0.06 (95% CI, 0.01 to 0.28; $P < .001$), while non-*Fusarium* cases had an odds ratio for perforation of 1.08 (95% CI, 0.48 to 2.43; $P = .86$). A total of 12 patients randomized to voriconazole had an increase of at least 2 mm in hypopyon size, while only 5 patients randomized to natamycin showed such an increase ($P = .09$) (**Table 6**).

When we analyzed BSCVA at 3 months making no special adjustment for TPK, we obtained similar findings. The mean BSCVA for patients randomized to receive voriconazole was 1.4 lines poorer at 3 months compared with those randomized to receive natamycin (regression coefficient = 0.14 logMAR; 95% CI, 0.02 to 0.25; $P = .02$). When individuals undergoing transplantation were assigned a value of 1.9 (instead of 1.7), the mean BSCVA for patients randomized to receive voriconazole was 1.8 lines poorer at 3 months compared with those randomized to receive natamycin (regression coefficient = 0.18 logMAR; 95% CI, 0.05 to 0.32; $P = .008$). Similar findings were obtained when adding a quadratic term in adjusting for baseline visual acuity. Linear mixed-effects regression of both 3-week and 3-month visual acuity as outcomes, using baseline visual acuity, treatment assignment, time, and the interaction between time and treatment as covariates, yielded similar findings (data not shown), while still including all available postrandomization visual acuity outcomes.

COMMENT

In MUTT I, we found significantly better visual acuity at 3 months in patients randomized to receive topical natamycin compared with those randomized to receive topical voriconazole. Voriconazole-treated cases were more likely to have a perforation and/or receive a therapeutic corneal transplant. Reepithelialization time and 3-month infiltrate or scar size were not significantly different between the 2 treatments. The difference in efficacy noted in this trial was primarily attributable to cases caused by *Fusarium* species.

Table 5. Multiple Linear Regression Predicting 3-Month Best Spectacle-Corrected Visual Acuity

Covariate	Coefficient, logMAR	SE	95% CI	*P* Value
Model with enrollment BSCVA and treatment arm				
Enrollment BSCVA	0.72	0.08	0.56 to 0.89	<.001
Natamycin vs voriconazole	−0.18	0.06	−0.30 to −0.05	.006
Model with interaction for *Fusarium* species				
Enrollment BSCVA	0.71	0.08	0.55 to 0.87	<.001
Natamycin vs voriconazole				
Fusarium species	−0.41	0.11	−0.61 to −0.20	<.001
Non-*Fusarium* species	−0.02	0.08	−0.17 to 0.13	.81

Abbreviation: BSCVA, best spectacle-corrected visual acuity.

Natamycin was significantly more successful at clearing culture positivity after 6 days than was voriconazole. Again, this difference was more pronounced among *Fusarium* species cases. Fewer than 10% of initially culture-positive patients in the natamycin group had a positive culture at 6 days, compared with more than 50% of patients randomized to voriconazole. Together with visual acuity and perforation or transplant results, these findings suggest that, in vivo, topical voriconazole is substantially less effective at clearing *Fusarium* species and should not be considered appropriate monotherapy for *Fusarium* keratitis.

Susceptibility studies with isolates from fungal keratitis had suggested that voriconazole could be an effective agent in the treatment of fungal keratitis. While minimum inhibitory concentrations for voriconazole were higher in *Fusarium* than *Aspergillus* species, voriconazole was still more effective against *Fusarium* species in vitro than natamycin and other antifungals.[10,11] A recent survey of corneal specialists suggested that while natamycin remains the most commonly used antifungal (96%), voriconazole was the preferred topical treatment (79%) over natamycin (55%).[9] This survey indicated that more physicians would use topical voriconazole as monotherapy in practice if it were more readily available. The results of this clinical trial were not consistent with the effectiveness of voriconazole suggested in vitro or the preference of corneal specialists for voriconazole. A previous trial found that chlorhexidine-treated cases reepithelialized more rapidly than natamycin-treated cases, although this trial used a lower dose of natamycin and was unmasked.[16] While chlorhexidine is a first-line agent for *Acanthamoeba*, it is rarely used for fungal keratitis in the United States.[9]

This study has several limitations. All patients were enrolled in South India. Patients in other regions may have different risk factors.[17-19] In North America, fungal keratitis has been linked to specific contact lens solutions.[3] In this trial, no contact lens wearers were enrolled. Most patients were agricultural workers who had trauma to their cornea. While other geographic regions also frequently isolate *Fusarium* and *Aspergillus* species, different strains of these organisms may have been present. This trial compared only topical monotherapies and did not assess whether topical voriconazole could add benefit when used in conjunction with natamycin. Also, we did not include a cost-effectiveness analysis, although it should be noted that topical voriconazole may currently be more expensive than topical natamycin. Moreover, this trial did not consider the use of oral voriconazole, which is currently being assessed in MUTT II.

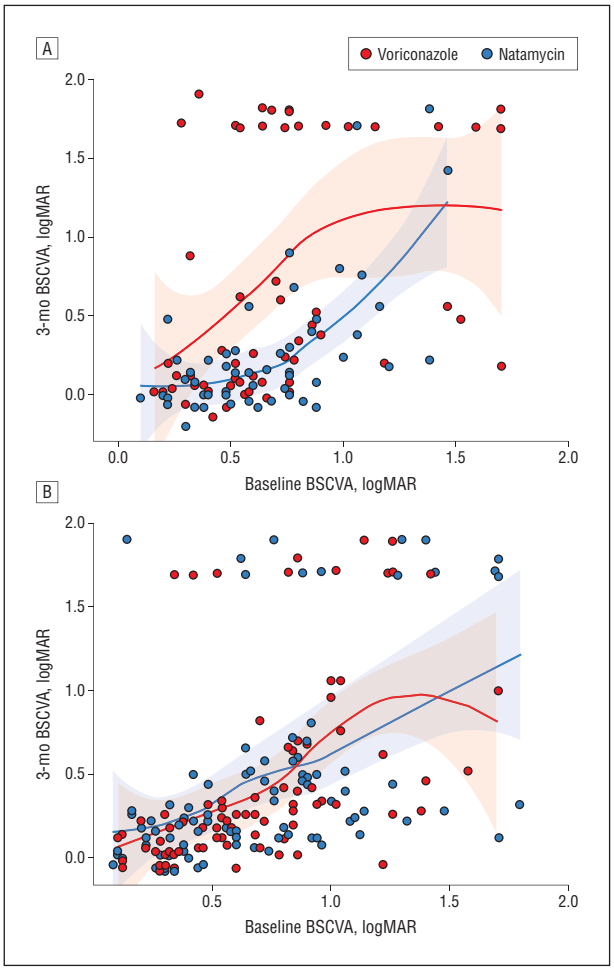

Figure 2. Three-month best spectacle-corrected visual acuity (BSCVA) vs baseline BSCVA for patients receiving voriconazole and natamycin, with *Fusarium* species (A) and non-*Fusarium* species (B) as the causative organism. The curve is a nonparametric locally weighted scatterplot smoothing regression fit, with the shaded bands indicating ±1 estimated SD. Patients who experienced perforation or corneal transplantation prior to the 3-month observation may have excellent visual acuity despite this adverse outcome and were assigned a low-vision score of 1.7 logMAR (or the 3-week BSCVA, whichever was worse). Observations over 1.5 logMAR were jittered for plotting.

Table 6. Adverse Events by Treatment Group

Adverse Event	No.			*P* Value[a]
	Voriconazole	Natamycin	Total	
Serious				
Corneal perforation	15	10	25	.31
TPK	29	13	42	.01
Corneal perforation and/or TPK	34	18	52	.02
Endophthalmitis	2	0	2	.50
Other serious ocular event thought to be related to study drug	0	0	0	NA
Death	1	1	2	>.99
Nonelective surgery, hospitalization, or loss of function	0	0	0	NA
Myocardial infarction or stroke	1	0	1	>.99
Nonserious				
Local allergic reaction	0	0	0	NA
>2-mm increase in hypopyon	12	5	17	.09
>50% Increase in infiltrate size	13	5	18	.06
Intraocular pressure ≥35 mm Hg for 1 wk despite therapy	0	0	0	NA
Progressive corneal thinning to ≤50% of thickness at enrollment	2	0	2	.25
Other nonserious	3	3	6	>.99

Abbreviations: NA, not applicable; TPK, therapeutic penetrating keratoplasty.
[a]Fisher exact test.

Topical natamycin is superior to topical voriconazole in filamentous keratitis. Monotherapy with the newer agent, topical voriconazole, cannot be recommended for filamentous fungal keratitis. Most of the difference between the 2 agents was found in *Fusarium* cases. This in vivo result is inconsistent with in vitro susceptibilities reported in earlier studies.[10,11]

Submitted for Publication: October 5, 2012; accepted October 8, 2012.
Published Online: December 10, 2012. doi:10.1001/jamaophthalmol.2013.1497
Author Affiliations: Aravind Eye Care System, Madurai (Drs N. V. Prajna, Mascarenhas, L. Prajna, and Srinivasan), Aravind Eye Care System, Pondicherry (Dr Krishnan), and Aravind Eye Care System, Coimbatore (Drs Rajaraman and Raghavan), India; Francis I. Proctor Foundation (Mss Oldenburg and Ray and Drs Porco, Acharya, and Lietman) and Departments of Ophthalmology (Drs McLeod, Acharya, and Lietman) and Epidemiology and Biostatistics (Drs Porco and Lietman), University of California, San Francisco; and Department of Surgery (Ophthalmology), Dartmouth Medical School, Lebanon, New Hampshire (Dr Zegans).
Correspondence: Thomas M. Lietman, MD, Department of Ophthalmology, University of California, San Francisco, 513 Parnassus Ave, Box 0412, San Francisco, CA 94143-0412 (tom.lietman@ucsf.edu).
Author Contributions: Dr Lietman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Mycotic Ulcer Treatment Trial Group: *Clinical Centers:* Aravind Eye Hospital, Madurai, Tamil Nadu, India: N. Venkatesh Prajna, MD (principal investigator), Lalitha Prajna, MD, Jeena Mascarenhas, MD, Muthiah Srinivasan, MD, Thirukkonda Subramanian Chandravathi, MA, R. Somu Saravanan, MA, Rajarathinam Karpagam, Malaiyandi Rajkumar, and Rajendran Mahalakshmi, MSc; Aravind Eye Hospital, Coimbatore, Tamil Nadu, India: Revathi Rajaraman, MD (site director), Anita Raghavan, MD, and P. Manikandan, MPhil; Aravind Eye Hospital, Pondicherry, Tamil Nadu, India: Tiruvengada Krishnan, MD (site director), and N. Shivananada, MD; Francis I. Proctor Foundation, University of California, San Francisco: Thomas M. Lietman, MD (principal investigator), Nisha R. Acharya, MD, MS (principal investigator), Stephen D. McLeod, MD, John P. Whitcher, MD, MPH, Salena Lee, OD, Vicky Cevallos, MT(ASCP), Catherine E. Oldenburg, MPH, Kieran S. O'Brien, MPH, and Kevin C. Hong, BA; *Data and Safety Monitoring Committee:* Marian Fisher, PhD (chair), Anthony Aldave, MD, Donald F. Everett, MA, Jacqueline Glover, PhD, K. Ananda Kannan, MD, Steven Kymes, PhD, and Ivan Schwab, MD; *Resource Centers:* Coordinating Center, Francis I. Proctor Foundation, University of California, San Francisco: Thomas M. Lietman, MD (principal investigator), Nisha R. Acharya, MD, MS (principal investigator), David Glidden, PhD, Stephen D. McLeod, MD, John P. Whitcher, MD, MPH, Salena Lee, OD, Kathryn J. Ray, MA, Vicky Cevallos, MT(ASCP), Catherine E. Oldenburg, MPH, Kevin C. Hong, BA, Kieran S. O'Brien, MPH; Project Office, National Eye Institute, Rockville, Maryland: Donald F. Everett, MA; Photography Reading Center, Dartmouth Medical School, Lebanon, New Hampshire: Michael E. Zegans, MD, and Christine M. Kidd, PhD.
Conflict of Interest Disclosures: None reported.
Funding/Support: This work was supported by grants U10 EY018573 (Dr Lietman) and K23 EY017897 (Dr Acharya) from the National Eye Institute and grants from That Man May See, the Harper/Inglis Trust, the South Asia Research Foundation, and Research to Prevent Blindness (Drs Lietman and Acharya). Natamycin and voriconazole were donated by Alcon and Pfizer, respectively.

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Online-Only Material: Listen to an author interview about this article, and others, at http://bit./y/LbUPaW.

This article is featured in the *JAMA Ophthalmology* Journal Club. Go to http://www.jamaophth.com to download teaching PowerPoint slides.

Additional Information: A full trial protocol can be accessed by contacting Dr Lietman.

REFERENCES

1. Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: a global perspective. *Bull World Health Organ*. 2001;79(3):214-221.
2. Srinivasan M, Gonzales CA, George C, et al. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, South India. *Br J Ophthalmol*. 1997; 81(11):965-971.
3. Chang DC, Grant GB, O'Donnell K, et al; Fusarium Keratitis Investigation Team. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. *JAMA*. 2006;296(8):953-963.
4. Khor WB, Aung T, Saw SM, et al. An outbreak of *Fusarium* keratitis associated with contact lens wear in Singapore. *JAMA*. 2006;295(24):2867-2873.
5. Margolis TP, Whitcher JP. *Fusarium*: a new culprit in the contact lens case. *JAMA*. 2006;296(8):985-987.
6. Bernal MD, Acharya NR, Lietman TM, Strauss EC, McLeod SD, Hwang DG. Outbreak of *Fusarium* keratitis in soft contact lens wearers in San Francisco. *Arch Ophthalmol*. 2006;124(7):1051-1053.
7. Gower EW, Keay LJ, Oechsler RA, et al. Trends in fungal keratitis in the United States, 2001 to 2007. *Ophthalmology*. 2010;117(12):2263-2267.
8. Wong TY, Ng TP, Fong KS, Tan DT. Risk factors and clinical outcomes between fungal and bacterial keratitis: a comparative study. *CLAO J*. 1997;23(4):275-281.
9. Loh AR, Hong K, Lee S, Mannis M, Acharya NR. Practice patterns in the management of fungal corneal ulcers. *Cornea*. 2009;28(8):856-859.
10. Lalitha P, Prajna N, Oldenburg C, et al. Organism, minimum inhibitory concentration, and outcome in a fungal corneal ulcer clinical trial. *Cornea*. 2012;31 (6):662-667.
11. Lalitha P, Shapiro BL, Srinivasan M, et al. Antimicrobial susceptibility of *Fusarium*, *Aspergillus*, and other filamentous fungi isolated from keratitis. *Arch Ophthalmol*. 2007;125(6):789-793.
12. Prajna NV, Mascarenhas J, Krishnan T, et al. Comparison of natamycin and voriconazole for the treatment of fungal keratitis. *Arch Ophthalmol*. 2010;128(6): 672-678.
13. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): design implications: AREDS report No. 1. *Control Clin Trials*. 1999;20(6):573-600.
14. Srinivasan M, Mascarenhas J, Rajaraman R, et al; Steroids for Corneal Ulcers Trial Group. Corticosteroids for bacterial keratitis: the Steroids for Corneal Ulcers Trial (SCUT). *Arch Ophthalmol*. 2012;130(2):143-150.
15. Wilhelmus KR, Gee L, Hauck WW, et al. Herpetic Eye Disease Study: a controlled trial of topical corticosteroids for herpes simplex stromal keratitis. *Ophthalmology*. 1994;101(12):1883-1896.
16. Rahman MR, Johnson GJ, Husain R, Howlader SA, Minassian DC. Randomised trial of 0.2% chlorhexidine gluconate and 2.5% natamycin for fungal keratitis in Bangladesh. *Br J Ophthalmol*. 1998;82(8):919-925.
17. 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):61-69.
18. Ibrahim MM, de Angelis R, Lima AS, et al. A new method to predict the epidemiology of fungal keratitis by monitoring the sales distribution of antifungal eye drops in Brazil. *PLoS One*. 2012;7(3):e33775.
19. Shah A, Sachdev A, Coggon D, Hossain P. Geographic variations in microbial keratitis: an analysis of the peer-reviewed literature. *Br J Ophthalmol*. 2011; 95(6):762-767.