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Mycotic Antimicrobial Localized Injection (MALIN): A Randomized Clinical Trial Evaluating Intrastromal Injection of Voriconazole

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Abstract

Objective: To determine if there is a benefit to adjuvant intrastromal voriconazole injections (ISV) for primary treatment of filamentous fungal keratitis.

Design: Outcome-masked, randomized controlled clinical trial

Study Participants: Patients presenting with moderate vision loss from a smear-positive fungal ulcer.

Intervention: Study eyes were randomized to topical natamycin plus ISV versus topical natamycin alone.

Main Outcome Measures: The primary outcome of the trial was microbiological cure on 3-day repeat culture. Secondary outcomes included microbiological cure on 7-day repeat culture, 3 week and 3 month best spectacle-corrected visual acuity (BSCVA), infiltrate and/or scar size, rate of perforation, therapeutic penetrating keratoplasty (TPK) and other adverse events.

Results: A total of 151 patients with smear positive ulcers were screened and 70 were enrolled at Aravind Eye Hospital, Pondicherry. Baseline cultures grew *Fusarium* in 19(27%), *Aspergillus* in 17(24%), other filamentous fungi in 19 (27%) and were negative in 13(19%). Those randomized to ISV had 1.82 times the odds of 3-day culture positivity after controlling for baseline culture status (95% CI 0.65 to 5.23; *P*=0.26, bias-corrected logistic regression) and 1.98 times the odds of a

positive 7 day culture, after controlling for baseline culture status (95% CI 0.69 to 5.91, P=0.20, bias-corrected logistic regression). Those randomized to ISV had 0.5 logMAR lines (approximately ½ Snellen lines) decreased visual acuity (95% CI −2.6 to 3.6; P=0.75) and 0.55 mm worse infiltrate and/or scar size at 3 month after controlling for baseline values (95% CI −0.13 to 1.25; P=0.11). ISV had 2.85-fold increased hazard of perforation after controlling for baseline infiltrate depth (95%CI 0.76 to 10.75; P=0.12) but no difference in rate of TPK (HR 0.95, 95% CI 0.44 to 2.04; P=0.90).

Conclusions: There appears to be no benefit to adding intrastromal voriconazole injections to topical natamycin in the primary treatment of moderate to severe filamentous fungal ulcers. Studies consistently suggest that voriconazole has a limited role in the treatment of filamentous fungal ulcers.

Trial Registration:

Précis

In this randomized clinical trial, moderate to severe fungal corneal ulcers receiving intrastromal injection of voriconazole plus topical natamycin did not experience improved outcomes compared with those receiving topical natamycin alone.

Introduction

Fungal corneal ulcers, because of their poor outcomes and the lack of evidence to guide treatment, present a therapeutic challenge to clinicians.[1] In the tropics, fungal infection can account for upwards of 50% of corneal ulcers.[1–3] In the United States fungal keratitis ranges from 35% of corneal ulcers in South Florida[4] to 4% in temperate climates such as Los Angeles.[5] The Mycotic Ulcer Treatment Trials I and II, were two NEI-funded randomized double-masked clinical trials that found topical natamycin to be superior to topical voriconazole and no additional benefit of adjuvant oral voriconazole. However, natamycin is fungistatic and has limited penetration into the corneal layers.[6] Although topical natamycin is the best available treatment for moderate to severe fungal keratitis at this time, outcomes remain poor. In MUTT II approximately 50% of study participants went on to full thickness corneal perforation or required a therapeutic penetrating keratoplasty (TPK). Therefore, we should continue to study other potential treatments or treatment combinations that may improve outcomes in fungal keratitis.

Voriconazole may still be an important adjunct in the treatment of fungal ulcers. *In vitro* studies suggest that voriconazole should have good efficacy against *Aspergillus* and *Fusarium*.[7] Intrastromal injection of voriconazole may provide steady state drug concentrations at the site of infection and avoid intervals of sub-therapeutic drug dosing. Additionally, there may be presenting characteristics, such as deep stromal involvement, which could predict a benefit from intrastromal voriconazole (ISV) injection. However, studies of ISV have yielded mixed results.[8–11] In this study we will evaluate the effectiveness of ISV in addition to topical natamycin treatment for the treatment of moderate to severe fungal keratitis.

Methods

Trial Design

Mycotic Antimicrobial Localized Injection (MALIN) was an institutionally-funded randomized, outcome-masked, two-arm clinical trial comparing clinical outcomes in study participants with moderate to severe smear-positive filamentous fungal corneal ulcers randomized to topical natamycin plus ISV versus topical natamycin alone. All study participants received medical therapy with topical natamycin, 5%, eye drops (Aurolab) every hour while awake, topical Moxifloxacin 0.5% (Aurolab) for prophylaxis every 2 hours while awake and homatropine 2% (Aurolab) 3 times daily.

Ethical approval was obtained from the University of California, San Francisco, Committee on Human Research and the Aravind Eye Care System Institutional Review Board, Pondicherry, India. Written informed consent was obtained from all participants, and the trial conformed to the Declaration of Helsinki.[12] The Data Safety and Monitoring Committee recommended one interim analysis to review safety, data quality and trial conduct.

Outcomes

The primary outcome of the trial was microbiological cure at 3-day on repeat culture. Secondary outcomes included best spectacle corrected visual acuity (BSCVA) at 3 weeks and 3 months, infiltrate and/or scar size at 3 weeks and 3 months, microbiological cure at 7-days, and adverse events including corneal perforation or the need for therapeutic penetrating keratoplasty (TPK).

Study Participants

All study participants were enrolled at Aravind Eye Hospital in Pondicherry, India. Consecutive patients who presented with smear-positive corneal ulcers and presenting visual acuity of 20/70 (logMAR 0.54) or worse were screened. Exclusion criteria included evidence of concomitant infection with herpes or bacteria, impending or frank perforation or limbal involvement, no light perception vision in the affected eye or visual acuity worse than 20/200 in the unaffected eye, age less than 18 or greater than 70, and patients that were cognitively impaired or unable to complete follow up. For the purposes of this study a moderate ulcer was defined as a 2–6 mm ulcer in a central or peripheral location involving the anterior two-thirds of the corneal stroma. Severe was defined as an ulcer greater than 6mm and involving the posterior stroma and/or with an endothelial plaque.

Interventions

After eligibility was confirmed and written informed consent was obtained, patients were randomized in a 1:1 fashion to receive ISV plus topical natamycin 5% (Aurolab, India) versus topical natamycin 5% alone. For those randomized to intrastromal injections, the procedure was scheduled in the operating room within 24 hours of enrolment in the study. Using aseptic techniques Voriconazole 0.5 mg/ml solution (VOZOLE PF; reconstituted with 2ml of lactated Ringer's solution. Aurolab, India) was prepared just prior to administration and loaded into a 1 ml tuberculin syringe with a 30-gauge needle. With the bevel down, the

needle was inserted obliquely starting in the adjacent uninvolved stroma to reach the infiltrate at the mid-stromal level (at the intended level for drug deposition). The drug was then injected and the amount of hydration of the cornea was used as a guide to assess the area saturated with medication. Four to six divided doses were given around the infiltrate/s to surround the entire circumference of the lesion/s. After the 3-day repeat corneal scraping, an additional two rounds of intrastromal injections were performed at 3 and 5 days post enrolment in the voriconazole injection arm only. All patients were hospitalized for the first 7 days so that all medications were directly observed and recorded by a health technician.

Study participants were examined by a masked study physician at baseline, 3 days, 1 week, 1 month and 3 months. A calibrated slit lamp biomicroscope was used to assess the epithelial defect size, infiltrate and/or scar dimensions and depth according to a protocol adapted from the Herpetic Eye Disease Study.[13] The presence of corneal perforation, hypopyon, or other ocular adverse event was also recorded. The study ophthalmologists were certified to ensure adherence to the study protocol. The patients were queried regarding serious and non-serious systemic adverse events.

Microbiological methods used for this study were adapted from a protocol used in the MUTT I which have been previously published in detail.[14] Baseline, 3 and 7-day scraping and cultures were obtained from the corneal ulcers of all study participants. Corneal scraping was performed with a Kimura spatula using aseptic technique and plated on to two separate microbiology slides for gram stain and KOH wet mount. Three further scrapings were directly inoculated on to sheep's blood agar, chocolate agar, potato dextrose or Sabourauds' agar for both bacterial and fungal culture. A positive fungal smear was defined as fungal elements seen under low-power magnification and reduced light. Positive fungal cultures were defined as light growth on any 2 media or moderate to heavy growth on 1 medium.

Best spectacle-corrected visual acuity was recorded at 4 meters at enrollment, 3 weeks, and 3 months by a masked refractionist certified for the study using a protocol adapted from the Age-Related Eye Disease Study using Early Treatment Diabetic Retinopathy Study (ETDRS) tumbling E charts (charts 2305 and 2305A; Precision Vision).[15] Low vision testing was also performed at a distance of 0.5m.

Masking

Study participants were not masked to their intervention but were asked not to share this information with any of the study personnel. While the surgeon performing intrastromal injection was not masked due to the nature of the intervention, the study physician performing repeat scraping and outcome assessment remained masked to treatment arm. The refractionist performing BSCVA and microbiologist analyzing culture results were also masked to treatment arm.

Statistical Analysis

The sample size was determined based on the primary end point of microbiological cure at 3 days. We anticipated that we would have 80% power to detect a difference in repeat culture status of 25% assuming a culture positive rate of 50% in the control group and 25% in the

intrastromal voriconazole group at 3 days with a two-tailed alpha of 0.05% and no loss to follow up (since participants were hospitalized after enrolment until the 3-day repeat cultures were taken). Participants were randomized using random block sizes in Microsoft Excel (KJR).

Baseline characteristics between the 2 arms were compared using Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables. The pre-specified primary analysis used a logistic regression model to assess microbiological cure at 3 days between groups (dichotomous culture positive or culture negative outcome) controlling for baseline culture status. Cox proportional hazards regression models were used to estimate the hazard of perforation or need for TPK associated with intrastromal injection plus medical therapy versus medical therapy alone while correcting for baseline infiltrate and/or scar size as a fixed effect. An identical Cox proportional hazards regression model with an interaction term for organism and treatment arm was used to evaluate the effect of intrastromal voriconazole on the pre-specified organism subgroups of *Aspergillus* species, *Fusarium* species, and all other organisms. A Wald test was performed to assess the significance of this interaction. Multiple linear regression was used to analyze BSCVA and infiltrate and/or scar size measured at 1 and 3 months with baseline measurements as co-variates. Fischer exact test was used to compare adverse events between arms.

For missing data for BSCVA due to TPK, we used the last observation carried forward (LOCF) or logMAR of 1.7 (Approximate Snellen equivalent 20/1000) if there was no LOCF data available. If there were missing data for infiltrate and/or scar or epithelial defect size resulting from a TPK, the LOCF prior to TPK was used. All analyses were conducted using Stata, version 13 (StataCorp), and were performed from October 5th to 12th.

Results

A total of 151 patients with smear positive ulcers were screened between October 7th, 2016 and July 25th, 2018 and 70 were randomized to topical natamycin 5% alone versus topical natamycin plus intrastromal voriconazole (ISV) injection (eFigure1). All study participants were enrolled at the Aravind Eye Hospital, Pondicherry. Follow up for the primary outcome of 3-day repeat culture was available for 69/70 (99%) of study participants, and 3-month follow up was available for 58/70 (83%). For those lost to follow up, home visits were performed to gather additional data. There was no evidence that loss to follow up was associated with baseline visual acuity or treatment arm. Baseline participant demographics and clinical characteristics are outlined in Table 1. No major differences between groups were identified.

Organisms isolated from baseline cultures are described in Table 2. *Fusarium* grew in 19(27%), Aspergillus in 17(24%), other filamentous fungi in 19 (27%) and cultures were negative in 13(19%). Baseline corneal cultures were negative in 5 (14%) of the topical natamycin only group and 8 (23%) of the ISV plus natamycin group.

At 3-days, 23(68%) of cultures were negative in the natamycin only group and 21 (60%) were negative in the natamycin plus ISV group. Those randomized to ISV had 1.44 times the

odds of 3-day culture positivity (*N*=69; 95% CI 0.55 to 3.83; *P*=0.46, bias-corrected logistic regression) in post-test only analysis, and 1.82 times the odd of 3-day culture positivity if baseline culture status was included in the model (95% CI 0.65 to 5.23; *P*=0.26, bias-corrected logistic regression). Those receiving ISV had 1.98 times the odds of a positive 7-day culture, after controlling for baseline culture status (95% CI 0.69 to 5.91, *P*=0.20, bias-corrected logistic regression). If the patient was baseline culture positive for *Fusarium* (*N*=19) those randomized to ISV had 3.33 fold increased odds of 3-day culture positivity (95% CI 0.25 to 45.11; *P*=0.37). If the patient was baseline culture positive for *Aspergillus* (*N*=16) those randomized to ISV had 0.75 fold increased odds of 3-day culture positivity (95% CI 0.04 to 14.58; *P*=0.85). If the patient was baseline culture positive for any other filamentous fungus and they were randomized to ISV, they had 3.6 fold increased odds of 3-day repeat culture positivity (95% CI 0.49 to 26.39; *P*=0.21).

Mean 3-week visual acuity was logMAR 1.23 (SD 0.65) in the natamycin only arm and logMAR 1.40 (SD 0.59) in the ISV arm. Mean 3-month visual acuity was 1.28 logMAR (SD 0.66) in the natamycin arm and 1.30 logMAR in the ISV plus natamycin arm. Those randomized to ISV had 1.6 logMAR (approximately 1 ½ Snellen lines) worse visual acuity at 3 weeks after controlling for baseline visual acuity (95% CI −1.2 to 4.4; *P*=0.25) and 0.5 logMAR (approximately ½ Snellen lines) decreased visual acuity after controlling for baseline visual acuity (95% CI −2.6 to 3.6; *P*=0.75).

At 3 weeks the infiltrate and/or scar size was 0.69 mm larger among those who were randomized to ISV after controlling for baseline measurements (95% CI 0.04mm to 1.33mm; *P*=0.04). Multiple linear regression models also found 0.55 mm worse infiltrate and/or scar size at 3 month infiltrate among those receiving ISV after controlling for baseline this was no longer statistically significant (95% CI −0.13 to 1.25; *P*=0.11).

Adverse events are outlined in Table 3. Overall there were 11 (16%) study participants who had full thickness corneal perforation, 8 (23%) in the ISV arm and 3 (9%) in the natamycin only arm. In a Cox proportional hazard model, those randomized to ISV had a 2.85-fold increased hazard of perforation after controlling for baseline infiltrate depth (95%CI 0.76 to 10.75; *P*=0.12). Twenty-seven (39%) eventuated to TPK, including 14 (40%) in the ISV arm and 13 (37%) in the natamycin only group. In a Cox proportional hazards model, those randomized to ISV exhibited a relative hazard of 0.95 for eventuating to TPK after controlling for baseline infiltrate and/or scar depth (95% CI 0.44 to 2.04; *P*=0.90). ISV conferred a 1.12 increased hazard of experiencing any adverse event, but this was not statistically significant (95% CI 0.44 to 2.88; *P*=0.81).

Discussion

We found no benefit to adjuvant ISV in this randomized clinical trial comparing intrastromal voriconazole (ISV) plus topical natamycin 5% to natamycin 5% alone for the primary treatment of moderate to severe filamentous fungal ulcers. Specifically, we found no improvement in microbiological cure rate at 3 or 7 days. Studies have suggested that in addition to providing an initial diagnosis, repeat culture can be used to assess response to treatment and is highly correlated with clinical outcomes such as visual acuity. Surrogate

outcomes such as these have become increasingly common in infectious disease trials.[16–19] Supporting our microbiological outcomes we also found no improvement in visual acuity and no reduction in the rate of perforation or need for TPK among those randomized to ISV. Scar size may be increased among those receiving ISV. In pre-specified subgroups looking at *Fusarium*, *Aspergillus* and other filamentous fungi, we found no evidence of a benefit to adjuvant ISV.

Although *in vitro* studies have suggested that voriconazole have good efficacy against filamentous fungi, clinical studies have been less encouraging. MUTT I demonstrated that topical voriconazole was inferior to topical natamycin, while MUTT II showed no benefit to adjuvant oral voriconazle in addition to topical natamycin. Theoretically, adjuvant ISV could be advantageous given natamycin's limited penetration into deep corneal stroma. Several prior case series have suggested that it could be beneficial.[8–10] One prior randomized controlled trial comparing intrastromal injection to topical voriconazole found significantly improved 3-month visual acuity in the topical voriconazole group.[11] However, these results were difficult to interpret, because in the intrastromal voriconazole arm there were more central ulcers than in the topical voriconazole arm and final scar size between the two groups was comparable, implying that intrastromal injection did not lead to worse scarring.

Limitations to this study include the fact that all patients enrolled in this study were from India, and the majority of infections were related to agricultural exposure and not contact lens wear, such as those seen in developed countries. Therefore, it is possible that organisms in this study exhibit different characteristics and response patterns to medications. Only a small number of each type of fungus was represented which may have made it difficult to detect a benefit of ISV for any particular organism. This study was powered to detect a difference in microbiological cure, a surrogate endpoint. Studies have suggested that in addition to providing an initial diagnosis, repeated culture can be used to assess response to treatment and is highly correlated with clinical outcomes such as visual acuity and outcomes such as these have become increasingly common in infectious disease trials.[16–19] Additionally clinical outcomes such as visual acuity, scar size, and rate of perforation and TPK in this study were supportive of the primary outcome.

Conclusions

There appears to be no benefit to adding intrastromal voriconazole injections to topical natamycin in the primary treatment of moderate to severe filamentous fungal ulcers. Studies consistently suggest that voriconazole has a limited role in the treatment of filamentous fungal ulcers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline demographic and clinical characteristics

Characteristic	Study Group	
	Standard Therapy (N = 35)	Intrastromal Voriconazole (N = 35)
Sex, No. (%)		
Male	18 (51)	26 (74)
Female	17 (49)	9 (26)
Age, median (IQR), y	55 (41, 62)	53 (42, 60)
Occupation, No. (%)		
Agriculture	15 (47)[a]	11 (33)[a]
Non-agriculture	17 (53)[a]	22 (67)[a]
Medication use at enrollment, No. (%)	23 (68)[a]	25 (71)
Trauma, No. (%)		
Stick	3 (9)	7 (20)
Leaf	1 (3)	2 (6)
Finger	1 (3)	0 (0)
Dust	4 (11)	3 (9)
Mud	4 (11)	4 (11)
Insect	1 (3)	5 (14)
Other	9 (26)	4 (11)
Unknown object[b]	2 (6)	0 (0)
None	10 (29)	10 (29)
Affected eye, No. (%)		
Right	17 (49)	15 (43)
Left	18 (51)	20 (57)
Visual acuity, median (IQR)		
LogMAR	1.7 (1.6, 1.8)	1.7 (1.6, 1.8)
Snellen	HM (CF, LP)	HM (CF, LP)
Ulcer location, No. (%)		
Central	32 (91)	30 (86)
Peripheral	3 (9)	5 (14)
Infiltrate and/or scar, median (IQR), mm[c]	5.1 (4.1, 6.4)	4.8 (4.0, 5.7)
Hypopyon, No. (%)		
No	13 (37)	16 (46)
<0.5 mm	7 (20)	6 (17)
>=0.5 mm	15 (43)	13 (37)
% Depth, No. (%)		
>0–33	10 (29)	13 (37)
>33–67	16 (46)	11 (31)
>67–100	9 (26)	11 (31)

Characteristic	Study Group	
	Standard Therapy (*N* = 35)	**Intrastromal Voriconazole** (*N* = 35)
Epithelial defect, median (IQR), mm[c]	4.1 (3.5, 5.5)	4.6 (3.8, 5.3)
Duration of symptoms, median (IQR), d	7 (4, 14)	7 (5, 15)
Systemic disease, No. (%)	5 (14)	7 (20)

[a]Missing data

[b]Includes chemicals, cow tail, finger nail, hay, iron ro d, red chili powder, sand, spark from fire, sugarcane leaf, and wood

[c]Geometric mean

Abbreviations: CF = count fingers, d = days, HM = hand motion, IQR = interquartile range, LogMAR = logarithm of the minimum angle, LP = light perception, mm = millimeters, No. = number, y = years

Table 2.

Baseline microbiologic culture results

Organism	No. (%)		Total (N = 70)
	Standard Therapy[a] (N = 34)	Intrastromal Voriconazole[a] (N = 34)	
Fusarium species	11 (31)	8 (23)	19
Aspergillus species	10 (29)	7 (20)	17
A. flavus	9 (26)	7 (20)	16
A. fumigatus	1 (3)	0 (0)	1
Curvularias species	0 (0)	4 (11)	4
Exserohilum species	1 (3)	1 (3)	2
Unidentified hyaline	2 (6)	3 (9)	5
Unidentified dematiaceous	5 (14)	3 (9)	8
Fungal culture negative	5 (14)	8 (23)	13

[a]Missing data for one patient in each arm

Abrreviations: A. = Aspergillus, No. = number

Table 3.

Adverse events by treatment group

Adverse Event	No. (%)		*P*-value
	Standard Therapy (*N* = 35)	**Intrastromal Voriconazole** (*N* = 35)	
Endophthalmitis	2 (6)	0 (0)	
Glaucoma	2 (6)	4 (11)	
Hypopyon	0 (0)	3 (9)	
Medication reaction	1 (3)	0 (0)	
Non-healing ulcer	0 (0)	3 (9)	
Perforation	3 (9)	8 (23)	
Progressive corneal thinning	0 (0)	1 (3)	
Therapeutic penetrating keratoplasty	13 (37)	14 (40)	
Total	21	33	0.81[a]

[a] Fisher's exact comparing number of people with any adverse event in each arm

Abbreviations: No. = number