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Risk factors for low vision related functioning in the Mycotic Ulcer Treatment Trial: a randomised trial comparing natamycin with voriconazole

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Abstract

Background/aims—The Mycotic Ulcer Treatment Trial I (MUTT I) was a double-masked, multicentre, randomised controlled trial, which found that topical natamycin is superior to voriconazole for the treatment of filamentous fungal corneal ulcers. In this study, we determine risk factors for low vision-related quality of life in patients with fungal keratitis.

Methods—The Indian visual function questionnaire (IND-VFQ) was administered to MUTT I study participants at 3 months. Associations between patient and ulcer characteristics and IND-VFQ subscale score were assessed using generalised estimating equations.

Results—323 patients were enrolled in the trial, and 292 (90.4%) completed the IND-VFQ at 3 months. Out of a total possible score of 100, the average VFQ score for all participants was 81.3 (range 0–100, SD 23.6). After correcting for treatment arm, each logMAR line of worse baseline visual acuity in the affected eye resulted in an average 1.2 points decrease on VFQ at 3 months (95% CI −1.8 to 0.6, p<0.001). Those who required therapeutic penetrating keratoplasty had an

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Competing interests None declared.

average of 25.2 points decrease on VFQ after correcting for treatment arm (95% CI −31.8 to −18.5, p<0.001). Study participants who were unemployed had on average 28.5 points decrease on VFQ (95% CI −46.9 to −10.2, p=0.002) after correcting for treatment arm.

Conclusions—Monocular vision loss from corneal opacity due to fungal keratitis reduced vision-related quality of life. Given the relatively high worldwide burden of corneal opacity, improving treatment outcomes of corneal infections should be a public health priority.

Trial registration number—Clinicaltrials.gov Identifier: NCT00996736.

INTRODUCTION

Evaluation of the relationship between therapeutic interventions and vision-related functioning is a recommendation of the Food and Drug Administration.[1] The National Eye Institute (NEI) has developed a visual function questionnaire (VFQ), which has been used to evaluate outcomes in macular degeneration, uveitis and cataracts.[2] The Indian VFQ (IND-VFQ) was field- tested and validated in a population of visually impaired and blind people living in India and is thought to better evaluate vision-related quality of life of patients living in developing countries.[3–5]

Fungal corneal ulcers present a therapeutic challenge to clinicians given their poor prognosis and lack of evidence to guide treatment.[6,7] In tropical regions, upwards of 50% of culture-proven infectious keratitis cases are due to fungal organisms.[6,8] The Mycotic Ulcer Treatment Trial I (MUTT I) was a NEI-funded double-masked multicentre randomised controlled trial which found that topical natamycin was superior to topical voriconazole for the treatment of filamentous fungal corneal ulcers, and in particular those culture-positive for *Fusarium* species.[9] As a secondary outcome, we administered the IND-VFQ 3 months after enrolment, and found that vision-related functioning was higher among those treated with natamycin compared with voriconazole.[10] In this ancillary study, we investigate which patient and ulcer characteristics were important predictors of vision-related functioning 3 months later.

METHODS

The methods for the MUTT I have been described in detail in previous publications.[9] Study sites included three hospitals of the Aravind Eye Care System in South India (Madurai, Pondicherry and Coimbatore) and the Francis I Proctor Foundation at the University of California, San Francisco, although all cases were enrolled in India. Individuals with smear-positive or culture-positive filamentous fungal corneal ulcers and baseline visual acuity of 20/40 to 20/400 (logMAR 0.3–1.3) were randomised to topical 5% natamycin or 1% voriconazole. Exclusion criteria included co-infection with bacteria, acanthamoeba or herpes; impending perforation; age less than 16 years; or visual acuity worse than 20/200 in the unaffected eye. Study participants were examined at enrolment, every 3 days (±1 day) until re-epithelialisation, at 3 weeks and at 3 months. The primary outcome was best spectacle-corrected visual acuity in the affected eye at 3 months. Prespecified secondary outcomes assessed at each study visit included infiltrate/scar size, infiltrate/scar depth, time to re-epithelialisation and corneal perforation.

The full 45-question IND-VFQ was a non-prespecified secondary outcome that was administered at the 3-month visit only. We analysed our data using recommendations from a Rasch analysis of the IND-VFQ by Finger *et al*.[5] This resulted in a questionnaire with four subscales (mobility subscale, 6 questions; activity limitation subscale, 10 questions; psychosocial impact subscale, 5 questions; visual function subscale, 7 questions) (see online supplementary table S1). Responses to each question were categorised on a 4-point Likert scale and equal weight was given to each response within the subscale.

We assessed for associations between patient and ulcer characteristics and IND-VFQ subscale score using generalised estimating equations to account for non-independence of within-participant subscale scores and controlling for treatment arm since this was found to be a significant predictor in a previous study.[10] Any characteristics found to be statistically significant (defined as $p<0.05$) were included in subsequent multivariate models. Model selection was performed with a backwards-stepwise algorithm until all covariates had a $p<0.2$. Holm-Šidák correction for multiple comparisons was applied to the final model to determine the statistical significance of each predictor with a significance level, α, set at 0.05.[11] Multiple linear regression was also performed to determine the subscale scores for each predictor separately, controlling for treatment arm. All analyses were conducted using Stata V.13.0.

RESULTS

A total of 323 patients were enrolled in MUTT I between 3 April 2010 and 31 December 2011, at which time enrolment was halted due to a significant reduction in corneal perforations in the natamycin arm. Three-month IND-VFQ results were available for 292 of 323 patients (90.4%). Loss to follow-up was not associated with any baseline characteristics, infecting organism or treatment arm (see online supplementary figure S1).

The average raw subscale scores were calculated out of a total possible score of 100. Raw scores on the mobility scale were very high with a median of 100 (IQR 69–100). The activity limitation (median of 97, IQR 73–100) and the psychosocial scores (median score 93, IQR 67–100) were good, while the visual function subscale score was overall decreased compared with the other three subscales (median score 76, IQR 62–91). Visual acuity improved markedly in the affected eye over the study period, from an average of 0.70 LogMAR (SD 0.38; 20/100 Snellen) at the baseline visit to 0.46 LogMAR (SD 0.57; about 20/60 Snellen) at the 3-month visit. In other words there was a mean decrease (improvement) of 0.24 LogMAR (SD 0.53; approximately 2.4 Snellen lines). Table 1 summarises the univariate analyses of the characteristics included in our study.

Table 2 outlines the characteristics included in the final multivariate statistical model. Although in univariate analysis depth of ulcer and perforation were predictors of 3-month VFQ, they were not significant in our multivariate model. However, study participants who required therapeutic penetrating keratoplasty (TPK) had significantly worse VFQ scores than those who did not, with those having undergone TPK scoring on average 25.5 points lower on VFQ (95% CI −32.0 to −18.9, $p<0.001$). There were a total of 24 perforations and 42 TPKs among study participants completing the VFQ. Sixty-three per cent (15/24) of the

perforations required TPK. As a sensitivity analysis, TPK was removed from the model since it was the only predictor that was not a baseline characteristic, however, this did not significantly change our findings for the other predictors.

Baseline visual acuity in the affected eye was a statistically significant predictor of IND-VFQ at 3 months. After controlling for treatment arm, each logMAR line of worsening baseline vision corresponded to 1.2 points decrease in 3-month VFQ (95% CI −1.8 to −0.6, p<0.001). Of particular note is the effect of visual acuity in the affected eye on psychosocial functioning in addition to the mobility or activity limitation. Table 3 outlines the four subscale scores for each of the characteristics in our multivariate model. Baseline visual acuity in the unaffected eye was included in the final model, although this was not statistically significant (each line of worse best spectacle-corrected visual acuity associated with 1.2 points decrease in VFQ, 95% CI −2.6 to 0.90, p=0.07).

Employment status was also a statistically significant predictor of 3-month VFQ. While only three study participants reported unemployment (representing approximately 1% of those completing VFQ), it was associated with 29 points decrease in VFQ on average, which was statistically significant (95% CI −47.7 to −10.3, p=0.002).

DISCUSSION

In this study we investigate risk factors for decreased vision-related quality of life in patients with filamentous fungal corneal ulcers. We found a statistically significant relationship between baseline visual acuity in the affected eye, the need for TPK and unemployment with vision-related quality of life as measured by IND-VFQ at 3 months after controlling for treatment arm.

Most of the literature regarding the relationship between visual acuity and vision-related functioning has been studied in diseases that affect both eyes, such as cataract, glaucoma and macular degeneration.[5,12–14] In these settings, vision-related functioning has often been more correlated with vision in the better-seeing eye.[15–17] This could lead to the conclusion that monocular vision loss does not greatly impact vision-related quality of life. However, previous research on unilateral eye diseases has not completely supported this notion. For example, a study of unilateral infectious keratitis found that vision-related quality of life was more correlated with vision in the worse-seeing eye.[18] Another study of patients with unilateral branch retinal vein occlusion found that visual acuity in the involved eye was most predictive of visual function.[19] A different study of unilateral central retinal vein occlusion (CRVO) found that although vision-related quality of life did not correlate with visual acuity in the affected eye, VFQ responses were lower than a reference group without eye disease—even among those patients with CRVO with excellent vision in the unaffected eye.[20] A study of patients with uveitis found that changes in the visual acuity of the worse eye was more predictive of vision-related quality of life than was visual acuity in the better eye.[21] A common feature of the unilateral eye diseases that have been studied is that they have a relatively sudden onset, and may therefore impact quality of life differently than a bilateral eye disease with gradual onset. The recent change in visual functioning in our study may account for the relative importance of the worse-seeing eye in determining vision-related

quality of life. It is possible that once a person has adapted to this change in vision, their vision-related quality of life will be most associated with visual acuity in the better-seeing eye. Studies of longer duration may help elucidate this possibility.

We found that monocular vision loss from fungal corneal ulcers had an impact on psychosocial functioning apart from its effect on mobility and activity limitation, especially among those with severe vision loss in the involved eye (table 3). It has been well established that poor vision is associated with depression.[1422–25] This may be exacerbated in developing countries where the visually impaired may be seen as a socioeconomic burden and there are fewer resources to aid them. Previous studies have suggested an increase in impact of visual disability in developing countries compared with developed countries.[318]

Employment status was a significant predictor of vision-related quality of life in our study. Socioeconomic status and lack of education have previously been shown to result in worse outcomes on VFQ.[51426–28] We did not look at income or educational background; however, unemployment is closely linked to poverty and lack of education. Although the impact of unemployment was large, the results should be interpreted with caution since only three study participants reported being unemployed. This finding warrants further investigation.

There has been some debate in the literature about whether outcomes in fungal ulcers are worse with *Fusarium*[29] or *Aspergillus*[7] *species. Aspergillus species* were the second most common causative organism in our population, representing 17% of all organisms. In many places in the world *Aspergillus* is the most common fungal pathogen isolated from corneal ulcers.[8] In our study, participants scored 7.3 points worse on VFQ if the aetiological organism was *Aspergillus* compared with *Fusarium* (p=0.03). Unfortunately MUTT 1 was unable to determine the optimal therapy for *Aspergillus* ulcers. Quality of life research may be an important way to determine priorities for future research.

Clinically significant changes on IND-VFQ have not yet been determined. One recent paper evaluating the responsiveness of NEI-VFQ to visual acuity changes concluded that a 4-point change in overall VFQ or a 5-point change in individual subscale score corresponded to a small clinically significant change.[17] Further study of the clinical relevance of changes on IND-VFQ is necessary; however, using the NEI-VFQ as a guide, an approximately three-line change in baseline visual acuity, unemployment or the need for TPK would all be considered clinically meaningful.

There are several limitations to our study. First, we did not collect quality of life data at the trial's baseline. Second, the IND-VFQ may not fully assess the monocular vision loss associated with corneal ulceration as it was validated in an Indian population of patients with cataract. Although the IND-VFQ was developed and validated locally, it is difficult for any visual function questionnaire to fully characterise the disability associated with decreased vision. Finally, these results may not be generalisable to other settings, and in particular, to more developed regions, since this trial was carried out on a population in rural southern India.

In summary, this study suggests that monocular vision loss from corneal opacity related to infectious keratitis has an effect on vision-related quality of life. This is important given that

corneal opacities are relatively common, making up the fourth leading cause of global blindness. Improving treatment outcomes of corneal infection should be a public health priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Univariate analysis for baseline predictors of IND-VFQ

Predictor	No. (%) or mean (±SD)* n=292	Coefficient (95% CI)	p Value
Baseline			
Age, years	47 (12.7))	−0.3 (−0.50 to −0.13)	0.001
Sex, male	165 (56.5)	−2.1 (−6.93 to 2.73)	0.40
Affected eye, right	156 (53.4)	−4.4 (−9.2 to 0.4)	0.07
Unemployed status	3 (1)	−35.4 (−58.8 to −12.0)	0.003
Visual acuity			
Affected eye, LogMAR	0.70 (0.39)	−25.4 (−31.0 to −19.8)	<0.001
Unaffected eye, LogMAR	0.06 (0.19)	−18.4 (−31.0 to −5.9)	0.004
Infiltrate/scar size, mm†	3.32 (1.2)	−4.7 (−6.6 to −2.8)	<0.001
Infiltrate depth‡		−4.7 (−7.8 to −1.6)	0.003
>0–33%	161 (55)		
>33–67%	103 (35)		
>67–100%	27 (9)		
Hypopyon (mm)		−5.7 (−8.8 to −2.6)	<0.001
None	189 (65)		
<0.5	55 (19)		
>0.5	48 (16)		
Organism§		−4.1 (−7.4 to −0.87)	0.013
Aspergillus	49 (17)		
Fusarium	115 (39)		
Other	128 (44)		
Follow-up			
Time to re-epithelialisation, days	12.7 (7.9)	−0.78 (−1.1 to −0.5)	<0.001
Perforation	24 (8)	−21.0 (−29.4 to −12.6)	<0.001
Therapeutic keratoplasty	42 (14)	−30.0 (−35.9 to −24.1)	<0.001

*Data expressed as number of patients (%) or mean (SD) unless otherwise specified.

†Geometrical mean of the longest diameter and longest perpendicular diameter in millimetres.

‡Expressed as a percentage of total corneal depth.

§*Aspergillus, Fusarium* or other species as aetiological organism of ulcer.

IND-VFQ, Indian visual function questionnaire.

Table 2

Multivariate analysis of predictors of IND-VFQ

Predictor	Coef (95% CI)	p Value
Age	−0.17 (−0.36 to 0.01)	0.06
Employment status *	−28.5 (−46.9 to −10.2)	0.002 †
Baseline visual acuity		
Affected eye	−1.2 (−1.8 to −0.6)	<0.001 †
Unaffected eye	−1.2 (−2.6 to 0.09)	0.07
Baseline infiltrate/scar size ‡	−2.1 (−4.0 to −0.2)	0.03
Organism §		0.09
Aspergillus	−7.3 (−13.8 to −0.79)	0.028
Fusarium	1.44 (−2.1 to 5.0)	0.43
Therapeutic penetrating keratoplasty	−25.2 (−31.8 to −18.5)	<0.001 †

Patient and ulcer characteristics that predict 3-month IND-VFQ scores calculated from a generalised estimating equation (GEE), allowing for non-independence of within-patient subscale scores.

* Study participant reports unemployment.

† Statistically significant after Holm-Šidák correction for multiple comparisons.

‡ Geometrical mean of the longest diameter and longest perpendicular diameter in millimetres.

§ Omnibus p value for organism categorised as *Aspergillus, Fusarium* or other.

IND-VFQ, Indian visual function questionnaire.

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Table 3

Multivariate analysis subscale score for baseline predictors of IND-VFQ

Subscale	Mobility		Activity limitation		Psychosocial		Visual function	
Predictor	**Coef (95% CI)**	**p Value**	**Coef (95% CI)**	**p Value**	**Coef (95% CI)**	**p Value**	**Coef (95% CI)**	**p Value**
Age	−0.18 (−0.34 to −0.01)	0.04	−0.17 (−0.31 to −0.02)	0.001	−0.15 (−0.40 to 0.10)	0.25	−0.22 (−0.45 to 0.003)	0.001
Employment status	−20.4 (−38.2 to −2.7)	0.02	−27.0 (−42.6 to −11.3)	0.001	−36.3 (−63.3 to −9.2)	0.009	−30.2 (−54.6 to −5.8)	0.02
BSCVA								
Affected	−1.3 (−1.8 to −0.7)	<0.001	−0.8 (−1.3 to −0.3)	0.002	−1.5 (−3.3 to −0.7)	<0.001	−1.2 (−5.0 to −2.0)	0.002
Unaffected	−0.6 (−1.6 to 4.4)	0.25	−1.0 (−2.0 to −0.7)	0.04	−1.7 (−3.4 to −0.3)	0.04	−1.7 (−3.2 to −2.3)	0.02
Baseline infiltrate/scar*	−0.97 (−2.7 to 0.75)	0.27	−1.3 (−2.7 to 0.23)	0.10	−2.2 (−4.8 to 0.4)	0.09	−3.8 (−6.2 to −1.5)	0.001
Organism†	−6.9 (−11.6 to −2.1)	0.005	−7.2 (−11.4 to −3.0)	0.001	−7.8 (−15.0 to −0.53)	0.035	−4.5 (−11.1 to 2.0)	0.17
TPK	−21.0 (−26.4 to −15.7)	<0.001	−22.5 (−27.2 to −17.7)	<0.001	−30.6 (−38.7 to −22.4)	<0.001	−26.1 (−33.5 to −18.7)	<0.001

*Geometrical mean of the longest diameter and longest perpendicular diameter in millimetres.

†*Aspergillus* versus non-*Aspergillus species* as aetiological organism of ulcer.

BSCVA, best spectacle-corrected visual acuity; IND-VFQ, Indian visual function questionnaire; TPK, therapeutic penetrating keratoplasty.