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The Steroids for Corneal Ulcers Trial (SCUT): secondary 12-month clinical outcomes of a randomized controlled trial

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Abstract

Purpose—To determine whether topical corticosteroids as adjunctive therapy for bacterial keratitis improves long-term clinical outcomes.

Design—Randomized placebo-controlled double-masked clinical trial.

Methods—This multicenter trial compared 1.0% prednisolone sodium phosphate to placebo in the treatment of bacterial keratitis among 500 patients with culture-positive ulcers receiving 48 hours of moxifloxacin before randomization. The primary endpoint was 3 months from enrollment, and 399 patients were evaluated at 12 months. The outcomes examined were best spectacle-corrected visual acuity (BSCVA) and scar size at 12 months. Based on previous results, regression models with adjustments for baseline status and/or causative organism were used for analysis.

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Results—No significant differences in clinical outcomes by treatment group were seen with the pre-specified regression models (BSCVA: −0.04 logMAR, 95%CI, −0.12 to 0.05, *P*=0.39; scar size: 0.03mm, 95% CI, −0.12 to 0.18, *P*=0.69). A regression model including a *Nocardia*-treatment arm interaction found corticosteroid use associated with a mean one-line improvement in BSCVA at 12 months among patients with non-*Nocardia* ulcers (−0.10 logMAR, 95%CI, −0.19 to −0.02, *P*=0.02). No significant difference was observed in 12-month BSCVA for *Nocardia* ulcers (0.18 logMAR, 95% CI, −0.04 to 0.41, *P*=0.16). Corticosteroids were associated with larger mean scar size at 12 months among *Nocardia* ulcers (0.47mm, 95% CI, 0.06 to 0.88, *P*=0.02) and no significant difference was identified by treatment for scar size for non-*Nocardia* ulcers (−0.06mm, 95%CI, −0.21 to 0.10, *P*=0.46).

Conclusions—Adjunctive topical corticosteroid therapy may be associated with improved long-term clinical outcomes in bacterial corneal ulcers not caused by *Nocardia* species.

Keywords

corneal ulcer; bacterial; corticosteroids; clinical trial

INTRODUCTION

The adjunctive use of topical corticosteroids in the treatment of bacterial keratitis continues to be controversial.[1–4] Though some fear the potential of corticosteroids to exacerbate infection, the anti-inflammatory effects of corticosteroids may decrease scarring and improve long-term visual outcomes. Prior to the Steroids for Corneal Ulcers Trial (SCUT), a lack of conclusive evidence deterred efforts to define optimal treatment practices. Previous experimental, animal, and observational studies found mixed results.[1, 5–11] Of three small randomized controlled trials, none had sufficient power to provide solid evidence of the efficacy of corticosteroids for bacterial corneal ulcers.[12–14]

In order to provide further evidence to guide treatment practices, the Steroids for Corneal Ulcers Trial (SCUT) assessed the effect of adjunctive corticosteroids on clinical outcomes in patients with bacterial corneal ulcers. The primary outcome of this trial revealed no benefit of adjunctive corticosteroids at 3 months from enrollment.[15] Beyond a possible delay in healing, no harm was found to result from the use of corticosteroids overall.[15] Sub-group analyses suggested that patients with more severe ulcers may have benefited from the addition of corticosteroids.[15] Further analyses indicated that corticosteroids may be associated with worse clinical outcomes in patients with ulcers caused by *Nocardia* species compared with patients with ulcers caused by other bacterial organisms.[16]

Overall, SCUT found no difference in clinical outcomes at 3 months between patients using corticosteroids versus placebo,[15] but differences may arise after a longer period of time. It is possible that clinical benefits with corticosteroids are not seen until later due to delayed healing or effects on subsequent corneal remodeling. On the other hand, ulcers in general may take more than 3 months to reach their visual potential.[17] SCUT was designed with a 12-month follow-up visit to examine such longer term effects. Here, we present the 12-month clinical outcomes of this trial.

METHODS

Trial Design

SCUT was a National Eye Institute-funded, randomized, placebo-controlled, double-masked multicenter clinical trial that compared clinical outcomes in patients receiving adjunctive topical corticosteroid or topical placebo in the treatment of bacterial corneal ulcers. Detailed

trial methods have been described elsewhere.[18] Briefly, 500 patients with culture-positive bacterial corneal ulcers received at least 48 hours of topical moxifloxacin, 0.5% (Vigamox, Alcon, Fort Worth, TX) before being randomized to receive either topical prednisolone phosphate, 1.0% (Bausch & Lomb Pharmaceuticals, Inc., Tampa, Florida), or topical placebo (sodium chloride, 0.9%, and preservative, prepared by Leiter's Compounding Pharmacy, San Jose, California). Specific details of sample size determination for this trial have been reported in depth previously.[18] Patients were randomized in a 1:1 ratio by center in random block sizes of 4, 6, or 8 using the previously described randomization allocation sequence.[18] As the placebo appeared identical to the prednisolone phosphate solution, double-masking of patient and examiner was achieved. Prospective institutional review board approval for this study was obtained from the Aravind Eye Care System's Institutional Review Board, Dartmouth-Hitchcock Medical Center Committee for the Protection of Human Subjects, and the University of California, San Francisco Committee on Human Research. Informed consent was obtained from all study participants. The trial was compliant with the Health Insurance Portability and Accountability Act, observed the Declaration of Helsinki, was approved by the Food and Drug Administration (IND #71,800), and was registered at clinicaltrials.gov (NCT00324168).

Study Participants

Eligible patients with culture-proven bacterial corneal ulcers were randomized to receive either topical prednisolone phosphate or placebo after receiving at least 48 hours of topical moxifloxacin. Complete eligibility criteria have been described in depth elsewhere.[18] In brief, major exclusion criteria included corneal perforation or impending perforation; evidence of fungus on potassium hydroxide preparation, Giemsa stain or culture; evidence of acanthamoeba by stain; evidence of herpetic keratitis by history or examination; use of a topical corticosteroid or systemic prednisolone during the course of the present ulcer; previous penetrating keratoplasty; and vision less than 6/60 in the fellow eye. Patients were enrolled at the Aravind Eye Care System (Madurai, Coimbatore, and Tirunelveli, India), the Dartmouth-Hitchcock Medical Center (Lebanon, New Hampshire), and the Francis I. Proctor Foundation for Research in Ophthalmology at the University of California, San Francisco.

Intervention

All patients received 1 drop of moxifloxacin every hour while awake for the first 48 hours, then every 2 hours until re-epithelialization, and then 4 times a day until 3 weeks from enrollment. The treatment regimen for the study drug (either prednisolone phosphate or placebo) consisted of 1 drop applied topically 4 times per day for 1 week after randomization, then twice a day for 1 week, and then once per day for 1week. If deemed medically necessary, treating physicians were allowed to discontinue or change any medications during the study.

Main Outcome Measures

The primary outcome for this trial, best spectacle-corrected visual acuity (BSCVA) at 3 months, has been reported.[15] As previously specified, patients were scheduled to return for an additional follow-up visit at 12 months.[15, 18] The outcomes of interest for this report are BSCVA at 12 months from enrollment, scar size at 12 months measured by slit lamp examination, and adverse events, including corneal perforation. As with all study visits, visual acuity was measured by refractionists certified for the study using a tumbling "E" chart at 4 m and logMAR visual acuity (charts 2305 and 2305A; Precision Vision, La Salle, Illinois). Visual acuity measurements were assessed based on the total number of letters read correctly. If fewer than 10 letters were read at 4 m, acuity was assessed at 1 m. If a patient read fewer than 10 letters at 1 m, counting fingers, hand motions, light perception, and no

light perception were used to assess low vision. Further detailed methods for outcome assessments have been reported elsewhere.[15, 18]

Statistical Methods

Patient characteristics at enrollment were compared by treatment arm for those patients who returned for follow-up at 12 months. To examine the potential effects of loss to follow-up between 3 and 12 month visits, enrollment characteristics and 12-month follow-up visit status among those with a 3-month visit were also compared by treatment arm. BSCVA between 3 and 12 months was also examined by treatment group and level of improvement in visual acuity. In all visual acuity analyses, for those patients who underwent therapeutic penetrating keratoplasty before follow-up visual acuity measurements, we utilized the last observation carried forward (LOCF) or 1.7 logMAR acuity, whichever was worse. Comparisons were made using Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables. All *P*-values were two-sided and $P<0.05$ was considered significant. All analyses were performed using Stata version 10.0 (StataCorp LP, College Station, Texas) or the R program (R Foundation for Statistical Computing, Vienna, Austria).

Only those visits that fell within the 12-month visit window (10–14 months from enrollment) were included in the analysis. For BSCVA at 12 months, the pre-specified analysis involved a linear regression model with enrollment BSCVA and treatment arm as covariates. After the SCUT 3 month results were reported, further analyses indicated that the model of this relationship could be improved. We used higher order polynomials to better fit the relationship between presentation and 12-month acuity, and we performed a sensitivity analysis with cubic splines to demonstrate that results were not dependent on the exact modeling technique. We also added an interaction term for *Nocardia* ulcers given the differential effects of corticosteroids previously reported among patients with *Nocardia* ulcers.[16] The twelve-month visual acuity was modeled using Gram-Schmidt orthogonal polynomials of the enrollment acuity. We chose the maximum polynomial degree (6) by cross-validation using a randomly chosen 20% of the data as a test set, conducting the regression on the remaining 80% of the data, using the resulting regression model to predict outcomes for the test set, and choosing the polynomial degree to minimize the squared error of prediction. Polynomial terms up to this maximum order were included in the final regression model, along with treatment, the *Nocardia* indicator, and the treatment-*Nocardia* interaction. The permutation *P*-value for the primary outcome was determined by Monte Carlo (10000 simulations), comparing the model with both treatment and *Nocardia*-treatment interaction to a model that included neither (likelihood ratio test, 2 degrees of freedom). Sub-groups of non-*Nocardia* ulcers were examined in a similar model. Scar size at 12 months was analyzed in a linear regression model with one additional covariate accounting for effect modification by *Nocardia* ulcers. Adverse events between the two groups were compared using Fisher's exact test.

Sensitivity analyses were conducted for BSCVA and scar size. BSCVA at 3 months and scar size at 3 months were reexamined using the linear regression models with the additional covariates. Hard contact lens-corrected visual acuity at 12 months was examined in a similar model. Another analysis utilized LOCF for patients lost to follow-up at 12 months and included data for those patients who had a 12-month study visit that fell outside of the pre-specified window. To further examine the appropriateness of the final model for BSCVA, a cubic spline function with 4 knots was used to correct for baseline BSCVA in the model at 12 months. Finally, variables in which in which significant differences ($P<0.05$) in baseline characteristics were noted between arms were added as covariates in the model of BSCVA at 12 months.

RESULTS

Between September 1, 2006, and February 22, 2010, 1769 patients were screened for the trial and 500 patients were enrolled with 250 patients randomized to receive topical corticosteroid and 250 to receive topical placebo (Supplemental Figure). Of the 500 enrolled patients, 399 (79.8%) returned for a follow-up visit within the 12-month window (10–14 months from enrollment). Among those with a 12-month visit within the pre-specified window, 202 (50.6%) patients were in the corticosteroid arm and 197 (49.4%) in the placebo arm. Of the 101 patients excluded from the 12-month analysis, 26 (25.7%) were excluded because their 12-month visit did not fall within the follow-up window (10–14 months from enrollment) and 75 (74.2%) were excluded because they did not return for a 12-month follow-up visit.

Overall, enrollment characteristics of patients with a 12-month follow-up visit were balanced between treatment arms (Tables 1 and 2). Among those patients who returned at 12 months, there were more males in the placebo arm (P=0.03). Compared to the placebo group, the corticosteroid group included more central corneal ulcers completely encompassing the 4-mm pupil (P=0.01). Similarly, among patients with a 3-month follow-up visit, the only significant differences in enrollment characteristics by treatment arm were noted for gender and ulcer location (P=0.02 for both comparisons). No statistically significant differences were found in the change in BSCVA from 3 to 12 months when visual acuity was examined as a categorical variable (Fisher's exact, P=0.96) or as a continuous variable (Wilcoxon rank sum, P=0.94). An additional 43 patients were considered lost to follow-up for analysis between 3 and 12 months, but no significant difference was observed when comparing 12-month visit status by treatment arm among those who had a 3-month follow-up visit (P=0.66). We were unable to detect statistically significant evidence of differential follow-up between 3 and 12 months among these patients for enrollment visual acuity (P=0.065) or enrollment scar size (P=0.32).

The pre-specified analysis found no significant differences in BSCVA or scar size between treatment arms (BSCVA: −0.04 logMAR, 95%CI, −0.12 to 0.05, P=0.39; scar size: 0.03mm, 95%CI, −0.12 to 0.18, P=0.69). For the primary analysis, a mean one-line improvement in BSCVA at 12 months was seen with corticosteroid use compared to placebo among patients with non-*Nocardia* ulcers (Table 3). This model also demonstrated that corticosteroids produce no significant effect on BSCVA at 12 months for ulcers caused by *Nocardia* species (Table 3). A similar model predicting contact lens-corrected visual acuity at 12 months, with baseline BSCVA and a *Nocardia*-treatment interaction term as covariates, produced comparable results (non-*Nocardia*: −0.09 logMAR, 95% CI −0.17to −0.004, P=0.039; *Nocardia*: 0.14 logMAR, 95% CI, −0.09 to 0.36, P=0.23).

A multiple linear regression model adjusted for *Nocardia* showed that, for patients with *Nocardia* ulcers, corticosteroid use was associated with larger scar sizes at 12 months compared to placebo (0.47mm, 95% CI, 0.06 to 0.88, P=0.02). For ulcers not caused by *Nocardia* species, a non-significant reduction in scar size was seen with corticosteroid use compared with placebo (−0.06mm, 95%CI, −0.21 to 0.10, P=0.46). Neither adding gender nor ulcer location (peripheral, partially covering 4mm circumference, completely covering 4mm circumference) as a covariate to the models altered these findings for BSCVA or scar size.

Further sensitivity analyses did not affect the 12-month results. The alternative method to correct for baseline visual acuity, a cubic spline function with 4 knots, demonstrated that visual acuity at 12 months for non-*Nocardia* ulcers was not dependent on our choice of baseline visual acuity correction (−0.11 logMAR, 95%CI, −0.19 to −0.02, P=0.02). Using

LOCF for patients lost to follow-up after the 3-month visit and including patients who had a 12-month visit outside the window did not alter the findings (non-*Nocardia*: −0.08 logMAR, 95% CI −0.16 to 0.003, *P*=0.059; *Nocardia*: 0.18 logMAR, 95% CI, −0.05 to 0.40, *P*=0.12). When the adjusted models were applied to the 3 month data, no significant differences in clinical outcomes by treatment arm were seen with the additional interaction term for *Nocardia*, though the effect sizes were similar to the 12 month results

Adverse events by treatment group for the first 3 months of the trial were previously reported.[15] No corneal perforations were reported between 3 and 12 months from enrollment. Five surgeries, including 1 optical penetrating keratoplasty and 4 cataract surgeries, were performed between 3 and 12 months. The penetrating keratoplasty patient was in the corticosteroid arm. During this time period, 2 (0.8%) corticosteroid patients died and 4 (1.6%) placebo patients died. These differences were not statistically significant (*P*=0.69) and no deaths were deemed related to study participation.

DISCUSSION

The previously reported primary outcome for SCUT found no significant difference in clinical outcomes at 3 months between patients receiving topical corticosteroid or placebo as adjunctive therapy in the treatment of bacterial corneal ulcers.[15] Secondary analyses of the 3-month data suggested that ulcers caused by *Nocardia* species fared worse with steroids.[16] At 12 months from enrollment, we did find evidence that corticosteroids may be associated with improved long-term visual outcomes among ulcers not caused by *Nocardia* species. Additionally, corticosteroid use may be associated with larger scar sizes among *Nocardia* ulcers. When the adjustment for potential differential effects among *Nocardia* ulcers was removed, however, significant differences between treatment arms were not detected for either outcome.

Some differences in enrollment characteristics were noted among patients with a 12-month follow-up visit when compared by treatment arm. Among those patients with a 12-month follow-up visit, gender and ulcer location differed significantly by treatment arm. When these variables were added to the final models, however, the results were unchanged. Additionally, we controlled for baseline visual acuity and baseline scar size in part to reduce the effect of differences in related variables like ulcer location on outcomes. We did not find a significant difference in follow-up by treatment arm between 3 and 12 months. Overall, the differences seen in enrollment characteristics by treatment arm are not likely to account for the differences in 3 and 12 month results.

The differential effect of corticosteroids on ulcers caused by *Nocardia* may account for the significant results found at 12 months. Previous case reports suggest treatment of *Nocardia* ulcers with corticosteroids may be associated with recurrent infection and prolonged healing time.[19, 20] SCUT data revealed that corticosteroids are associated with larger scar sizes in *Nocardia* cases.[16] A minimum inhibitory concentration (MIC) analysis with SCUT data also found that *Nocardia* species had among the highest MICs to moxifloxacin and that high MICs were associated with worse clinical outcomes.[21] These analyses were not conducted until after the results at 3 months were reported, so it may be that the separation of *Nocardia* ulcers at 12 months is responsible for the differences in results. However, when an interaction term for *Nocardia* and treatment is included in the 3 month models, no significant differences are found.

Thus it is also possible that corticosteroids require longer periods of time to reveal clinical benefits. This may be due to a number of reasons, including delayed re-epithelialization and the effect of corticosteroids on the level of corneal inflammation and tissue damage at the

time of infection that subsequently influences corneal remodeling. The SCUT pilot study found significantly delayed re-epithelialization among patients treated with corticosteroids.[13] Overall, the main trial did not find a difference in the rate of healing between treatment arms among patients whose re-epithelialization occurred within 21 days from enrollment.[15] However, among patients with an epithelial defect at 21 days or later from enrollment, a higher proportion had received corticosteroids.[15] Corticosteroids may also influence scar density by reducing immune-mediated tissue damage.[4] Such findings may indicate that corticosteroids are associated with delayed clinical benefits that are not yet seen at 3 months.

The major strengths and limitations of this trial have been previously discussed in depth.[15] Although the sample size was large, it was not powered to detect an effect among sub-groups. It is also possible that the relatively moderate corticosteroid regimen contributed to the similar outcomes among treatment groups overall. Other limitations of this study include the potentially limited generalizability of these results given the large proportion of Indian patients. This is especially important when considering the differential effect on *Nocardia* ulcers, which are rarely reported in the United States and Europe.[22–24] However, the other prevalent organisms in this trial are commonly reported in the United States and Europe. These results are relevant to such patients, as corticosteroids may improve visual outcomes in patients with non-*Nocardia* ulcers. Additional limitations include the choice of outcomes. The study was not designed to address the effect of steroids on scar density, which may affect visual outcomes. Some have suggested that different outcomes such as resolution of keratitis or duration of medical treatment would be more conducive to examining sub-groups like *Nocardia* ulcers.[25] Future studies could use imaging methods such as anterior segment optical coherence tomography or Scheimpflug imaging to quantify outcomes like scar density.

Corticosteroids may be associated with improved clinical outcomes after extended periods among ulcers not caused by *Nocardia.* These results provide further evidence of the need to be particularly cautious when considering corticosteroid use for certain ulcers and highlight the importance of using microbiological results in treatment decisions. Further work could confirm any long-term benefit of adjunctive corticosteroid use in the treatment of bacterial corneal ulcers among specific subgroups of ulcers, excluding those ulcers caused by *Nocardia* species.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

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Dr. M. Srinivasan is a cornea specialist and Professor of Ophthalmology. He has served as the Director of the Aravind Eye Hospitals in Madurai, India since 2005 and as the President of the Eye Bank Association of India since 2007. Dr. Srinivasan has extensive experience in corneal ulcer research in both clinical and field settings. He is a faculty member at the Aravind Eye Hospital and the P.G. Institute of Ophthalmology.

Table 1

Baseline demographics and risk factors by treatment arm among patients with a 12-month follow-up visit in the Steroids for Corneal Ulcers Trial (N=399[a])

Characteristic	*Placebo*		*Steroid*		*Total*		*P-value*
	N or median	% or IQR[b]	N or median	% or IQR[b]	N or median	% or IQR[b]	
Gender							
Male	118	59.9	98	48.5	216	54.1	0.03
Enrollment Site							
India	192	97.5	197	97.5	389	97.5	1.00
United States	5	2.5	5	2.5	10	2.5	
Age (years)	50	(40–60)	52	(40–61)	51	(40–60)	0.67
Occupation							
Manual Labor – Agriculture	93	47.2	87	43.1	180	45.1	0.36
Manual Labor – Non-agriculture	40	20.3	38	18.8	78	19.5	
Professional/Business/Service	18	9.1	13	6.4	31	7.8	
Domestic work	10	5.1	16	7.9	26	6.5	
Semi-skilled/Skilled labor	9	4.6	7	3.5	16	4.0	
Not working[c]	27	13.7	41	20.3	68	17.0	
Medication use at enrollment[d]							
Topical antibiotics	63	32.0	73	36.1	136	34.1	0.40
Other topical ocular drops[e]	42	21.3	49	24.3	91	22.8	0.55
Unspecified topical drops	44	22.3	42	20.8	86	21.6	0.72
Native medicines[f]	2	1.0	4	2.0	6	1.5	0.69
Systemic antibiotics	3	1.5	4	2.0	7	1.8	1.00
Systemic aspirin/NSAIDs[g]	5	2.5	5	2.5	10	2.5	1.00
Other systemic	6	3.0	9	4.5	15	3.8	0.60
Objects that caused trauma or injury							
Vegetative matter/Wood	67	34.0	80	39.6	147	36.8	0.26
Metal/Other[h]	52	26.4	44	21.8	96	24.1	0.29
Unknown object	16	8.1	10	5.0	26	6.5	0.23

Characteristic	*Placebo*		*Steroid*		*Total*		*P-value*
	N or median	**% or IQR[b]**	**N or median**	**% or IQR[b]**	**N or median**	**% or IQR[b]**	
Contact lens	3	1.5	4	2.0	7	1.8	1.00
Total	197	100.0	202	100.0	399	100.0	-

[a] Includes only those participants with a 12-month follow-up visit within the pre-specified window of 10–14 months from enrollment

[b] Inter-quartile range

[c] Includes unemployed, retired, etc.

[d] Some patients were taking more than 1 medication at enrollment

[e] Includes topical antifungals, dilating drops, glaucoma medication, and lubricating drops

[f] Includes castor oil, goat's milk, breast milk, and coconut oil

[g] Non-steroidal anti-inflammatory drugs

[h] Includes dust, finger, sand, cow's tail, and insect

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Table 2

Baseline clinical characteristics by treatment arm among patients with a 12-month follow-up visit in the Steroids for Corneal Ulcers Trial (N=399[a])

Characteristic	*Placebo*		*Steroid*		*Total*		*P-value*
	N or median	% or IQR[b]	N or median	% or IQR[b]	N or median	% or IQR[b]	
Total	197	100.0	202	100.0	399	100.0	-
Affected Eye							
Right	101	51.3	93	46.0	194	48.6	0.32
Left	96	48.7	109	54.0	205	51.4	
Visual Acuity (logMAR)	0.74	(0.36–1.44)	0.74	(0.34–1.70)	0.74	(0.34–1.70)	0.32
Infiltrate/Scar Size (mm)[c]	2.61	(1.90–3.79)	2.65	(1.90–4.08)	2.65	(1.90–3.95)	0.58
Ulcer Location[d]							
Entirely in periphery	36	18.3	22	10.9	58	14.5	0.01
Partially covering 4 mm circle	130	66.0	128	63.4	258	64.7	
Completely fills 4 mm circle	31	15.7	52	25.7	83	20.8	
Hypopyon	114	57.9	107	53.0	221	55.4	0.37
Depth							
>0–33%	88	44.7	87	43.1	175	43.9	0.74
>33–67%	57	28.9	66	32.7	123	30.8	
>67–100%	51	25.9	49	24.3	100	25.1	
Epithelial Defect (mm)[c]	1.90	(1.20–3.00)	2.00	(1.20–3.15)	2.00	(1.20–3.00)	0.68
Duration of Symptoms (days)	4	(3–7)	4	(3–7)	4	(3–7)	0.55
Ocular Surface Disease[e]	20	10.2	17	8.4	37	9.3	0.61
Dacryostenosis/Dacryocystitis	46	23.4	36	17.8	82	20.6	0.18
Pre-existing corneal abnormalities[f]	7	3.6	7	3.5	14	3.5	1.00
Pre-existing lid/lash abnormalities[g]	2	1.0	4	2.0	6	1.5	0.69
Systemic Disease[h]	9	4.6	11	5.4	20	5.0	0.82

[a] Includes only those participants with a 12-month follow-up visit within the pre-specified window of 10–14 months from enrollment

[b] Inter-quartile range

[c] Geometric mean of the longest diameter and longest perpendicular to that diameter in millimeters

[d] Excludes those patients with no photograph

[e] Includes meibomitis, dry eye, blepharitis, neurotrophic cornea, rosacea, and atopic disease

[f] Includes corneal degeneration, spheroidal degeneration, climactic droplet keratopathy, bullous keratopathy, epithelial hyperplasia, lattice dystrophy, Fuchs' dystrophy, and old scar due to keratitis

[g] Includes ectropion of the lower eyelid, Bell's palsy, eyelid laxity, lagophthalmos, eyelid scars, and madarosis

[h] Includes diabetes mellitus, asthma, Hansen's disease, eczema, psoriasis, human immunodeficiency virus, ichthyosis, hypertension, and malnutrition

Table 3

Association between corticosteroids and logMAR best spectacle-corrected visual acuity (BSCVA) at 12 months by causative organism in the Steroids for Corneal Ulcers Trial[a]

Covariate	Estimate (logMAR)	Standard Error	95% Confidence Interval	*P*-value
Steroid (vs. Placebo)				
Nocardia species	0.18	0.11	−0.04 to 0.41	0.10
Non-*Nocardia* species	−0.10	0.04	−0.19 to −0.02	0.02
Gram-positive	−0.10	0.05	−0.20 to 0.004	0.06
Gram-negative	−0.11	0.08	−0.27 to 0.05	0.16

[a]The regression model predicting 12-month logMAR BSCVA included polynomial terms for enrollment BSCVA and covariates for treatment arm, *Nocardia*, and the treatment-*Nocardia* interaction. The maximum power chosen by cross validation (10000 repetitions) was 6 and the overall permutation *P*-value including treatment and the treatment-*Nocardia* interaction (10000 simulations) was 0.02.