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ONLINE FIRST

Corticosteroids for Bacterial Keratitis

The Steroids for Corneal Ulcers Trial (SCUT)

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Objective: To determine whether there is a benefit in clinical outcomes with the use of topical corticosteroids as adjunctive therapy in the treatment of bacterial corneal ulcers.

Methods: Randomized, placebo-controlled, double-masked, multicenter clinical trial comparing prednisolone sodium phosphate, 1.0%, to placebo as adjunctive therapy for the treatment of bacterial corneal ulcers. Eligible patients had a culture-positive bacterial corneal ulcer and received topical moxifloxacin for at least 48 hours before randomization.

Main Outcome Measures: The primary outcome was best spectacle-corrected visual acuity (BSCVA) at 3 months from enrollment. Secondary outcomes included infiltrate/scar size, reepithelialization, and corneal perforation.

Results: Between September 1, 2006, and February 22, 2010, 1769 patients were screened for the trial and 500 patients were enrolled. No significant difference was observed in the 3-month BSCVA (–0.009 logarithm of the minimum angle of resolution [logMAR]; 95% CI, –0.085 to 0.068; $P = .82$), infiltrate/scar size ($P = .40$), time to reepithelialization ($P = .44$), or corneal perforation ($P > .99$). A significant effect of corticosteroids was observed in subgroups of baseline BSCVA ($P = .03$) and ulcer location ($P = .04$). At 3 months, patients with vision of counting fingers or worse at baseline had 0.17 logMAR better visual acuity with corticosteroids (95% CI, –0.31 to –0.02; $P = .03$) compared with placebo, and patients with ulcers that were completely central at baseline had 0.20 logMAR better visual acuity with corticosteroids (–0.37 to –0.04; $P = .02$).

Conclusions: We found no overall difference in 3-month BSCVA and no safety concerns with adjunctive corticosteroid therapy for bacterial corneal ulcers.

Application to Clinical Practice: Adjunctive topical corticosteroid use does not improve 3-month vision in patients with bacterial corneal ulcers.

Trial Registration: clinicaltrials.gov Identifier: NCT00324168

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THE USE OF TOPICAL CORTICOSTEROIDS as adjunctive therapy in the treatment of bacterial corneal ulcers has been debated extensively during the past few decades.[1-3] Corticosteroids are thought to reduce immune-mediated damage and have been shown to be beneficial in some systemic bacterial infections.[4-6] The American Academy of Ophthalmology suggests that although there may be a role for corticosteroids in the treatment of bacterial corneal ulcers, there is insufficient evidence to make an official recommendation.[7] To date, the only data available to guide decisions are the results of animal and retrospective studies and of 3 small clinical trials[8-10] that were underpowered to answer the question definitively. The primary objective of the Steroids for Corneal Ulcers Trial (SCUT) is to assess the effect of adjunctive topical corticosteroids on clinical outcomes in patients with bacterial corneal ulcers. In this report, we present the primary outcome and the main outcomes of the trial.

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Group Information: The Steroids for Corneal Ulcers Trial Clinical centers, committees, and resource centers are listed at the end of this article.

METHODS

TRIAL DESIGN

The SCUT is a National Eye Institute–supported randomized, placebo-controlled,

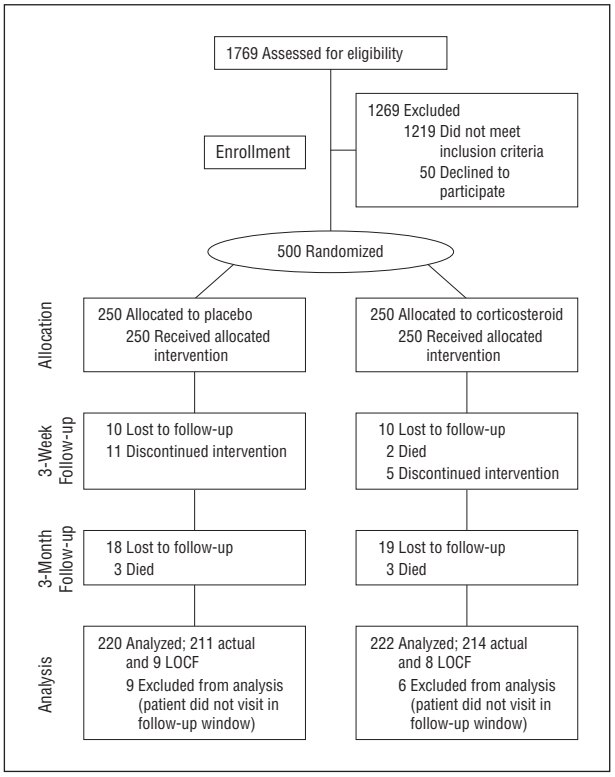

Figure 1. Consolidated Standards for Reporting Trials flowchart. LOCF indicates last observation carried forward.

double-masked, multicenter clinical trial comparing clinical outcomes in patients with bacterial corneal ulcers receiving topical moxifloxacin, 0.5% (Vigamox; Alcon/Novartis AG, Basel, Switzerland), and topical prednisolone sodium phosphate, 1.0% (Bausch & Lomb, Incorporated, Tampa, Florida) or topical placebo (sodium chloride, 0.9%, and preservative, prepared by Leiter's R_X Pharmacy, San Jose, California). Specific methods for the trial have been previously reported in depth.[11] Briefly, a sample size of 500 patients (250 per arm) was estimated to have 80% power to detect a 0.20–logarithm of the minimum angle of resolution (logMAR) (2 lines of visual acuity) difference in best spectacle-corrected visual acuity (BSCVA) 3 months after enrollment between the 2 study arms, assuming an SD of 0.65 logMAR for 3-month BSCVA.[9] The calculation assumed an α error of .05, a 2-tailed test, and 20% dropout rate. Participants were randomized in a 1:1 ratio. The randomization allocation sequence was generated as previously described.[11] Double masking (of the patient and the examiner) was achieved because the placebo was identical in appearance to the prednisolone sodium phosphate solution. Only the study biostatisticians were not masked. Institutional review board approval was granted by the Aravind Eye Care System's Institutional Review Board, the 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, adhered to the tenets of the Declaration of Helsinki, and was registered at clinicaltrials.gov (NCT00324168).

INTERVENTION

Patients were randomized to receive topical prednisolone sodium phosphate, 1.0%, or placebo after a cornea culture that tested positive for bacteria and after they had received 48 hours of topical moxifloxacin. The prednisolone sodium phosphate and placebo regimens consisted of 1 drop applied topically 4 times per day for 1 week after enrollment, then twice a day for 1 week, and then once a day for 1 week. The moxifloxacin treatment regimen for both arms consisted of 1 drop applied topically every hour while awake for the first 48 hours, then 1 drop applied every 2 hours until reepithelialization, and then 4 times a day until 3 weeks from enrollment. Treating physicians were allowed to change or discontinue the use of any medications, including the antibiotic and study medication, if they thought it was medically necessary.

STUDY PARTICIPANTS

Eligible patients had a culture-positive bacterial ulcer and had received at least 48 hours of topical moxifloxacin before randomization. Complete microbiological methods have been described previously.[11] 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. Complete inclusion and exclusion criteria have been described previously.[11] Enrollment centers included 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.

MAIN OUTCOME MEASURES

Patients were evaluated at baseline, every 3 days ± 1 day until reepithelialization, at 3 weeks, and at 3 months. The primary outcome of the trial was BSCVA at 3 months from enrollment using a tumbling E chart. Secondary outcomes include BSCVA at 3 weeks from enrollment; infiltrate/scar size at 3 weeks and 3 months measured by slitlamp examination; rate of adverse events, including corneal perforation; and time to reepithelialization. Specific methods for how these outcomes were assessed have been previously described.[9,11,12]

INTERIM MONITORING

We performed 11 interim reviews for safety, data quality, and trial conduct. A single review for efficacy was performed after approximately 250 of the 3-month visits had been completed. Interim reviews used the Lan-DeMets flexible spending approach to preserve the α level for the primary outcome.

STATISTICAL ANALYSES

The primary analysis considered only visits completed within the window period (2.5-5.0 months for the 3-month visit and 2.5-5.0 weeks for the 3-week visit). The analysis for BSCVA (in logMAR) at each time point used linear regression with terms for study treatment and enrollment BSCVA in the affected eye. Infiltrate/scar size analyses were conducted similarly. Time to reepithelialization was analyzed with a Cox proportional hazards regression model for the treatment group adjusted for baseline epithelial defect size. Continuous variables were compared using Wilcoxon rank sum tests, and proportions were compared using the Fisher exact test. All *P* values were 2-sided. Detailed methods on assignment of logMAR visual acuity for low vision and data handling after a thera-

Table 1. Baseline Characteristics Between Treatment Groups

Characteristic	No. of Patients[a]			*P* Value
	Placebo	Corticosteroid	Total	
Sex				
Male	147	126	273	.24[b]
Female	103	124	227	
Enrollment site				
India	242	243	485	.97[b]
United States	8	7	15	
Age, median (25th-75th percentile), y	54.5 (40.0-61.0)	52.0 (40.0-62.0)	53.0 (40.0-61.0)	.80[c]
Occupation				
Manual labor: agriculture	113	107	220	
Manual labor: nonagriculture	54	46	100	
Not working[d]	38	49	87	.45[b]
Professional, business, or service	22	17	39	
Domestic work	13	21	34	
Semiskilled or skilled labor	10	10	20	
Medication use at enrollment[e]				
Topical antibiotics	80	85	165	.70[b]
Other topical ocular drops[f]	50	58	108	.45[b]
Unspecified topical drops	60	54	114	.59[b]
Indigenous medicinal substances[g]	2	4	6	.67[b]
Systemic antibiotics	3	4	7	>.99[b]
Systemic aspirin or NSAIDs	7	8	15	>.99[b]
Other systemic	7	10	17	.62[b]
Object that caused the trauma or injury				
Vegetative matter or wood	89	99	188	.41[b]
Metal or other[h]	66	52	118	.17[b]
Unknown	18	15	33	.72[b]
Contact lens	3	5	8	.72[b]

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.
[a] Expressed as number of patients unless otherwise specified.
[b] Fisher exact test.
[c] Wilcoxon rank sum test.
[d] Includes unemployed, retired, and so forth.
[e] Some patients were taking more than 1 medication at enrollment.
[f] Includes topical antifungals, dilating drops, glaucoma medication, and lubricating drops.
[g] Includes castor oil, goat's milk, breast milk, and coconut oil.
[h] Includes dust, finger, sand, cow's tail, and insect.

peutic penetrating keratoplasty have been described elsewhere.[11] Prespecified sensitivity analyses for the primary outcome were as follows: per protocol analysis (restricted to only patients who completed their course of study medication); correcting for baseline ulcer location; including patients who visited outside their follow-up window; and excluding patients who had a change or addition to their antibiotic regimen within the first 3 weeks after enrollment.

A series of prespecified subgroup comparisons were performed to determine whether a differential effect of corticosteroids existed in subgroups of baseline characteristics. Significance was assessed by testing for statistical significance of the product terms for the interaction; we used an omnibus test for interactions over nonordered subgroups and a trend test for interactions over ordered subgroups.[13] Only if this omnibus or trend test was significant did we report specific tests as significant. Prespecified subgroups included baseline BSCVA (<20/40, 20/40 to 20/800, and counting fingers or worse), geometric mean of baseline infiltrate/scar size (0-1.90, 1.91-2.70, 2.71-4.06, and 4.07-8.90 mm), infiltrate depth (>0%-33%, >33%-67%, and >67%-100%), and ulcer location (completely filling the 4-mm central artificial pupil, partially filling the 4-mm central pupil, and entirely in the periphery). All statistical analyses were performed using STATA statistical software, version 10.0 (StataCorp LP, College Station, Texas).

RESULTS

Between September 1, 2006, and February 22, 2010, 1769 patients were screened for the trial and 500 patients were enrolled. Common reasons for ineligibility among the 1269 patients include impending perforation (n=316, 24.9%), history of a corneal scar in the affected eye (n=123, 9.7%), and vision worse than 6/60 in the fellow eye (n=119, 9.4%). Two hundred fifty patients were randomized to receive topical corticosteroid, and 250 received placebo (**Figure 1**). Four hundred forty-two patients (88.4%) returned for their 3-month follow-up visit within the specified visit window and were included in the analysis. Fifteen patients (3.0%) were excluded from the analysis because they did not return for follow-up in the visit window, and 43 (8.6%) did not return for a 3-month follow-up visit.

Overall, enrollment characteristics were well balanced between the 2 treatment arms (**Table 1** and **Table 2**). More central corneal ulcers encompassing the entire 4-mm pupil were observed in the corticosteroid group than in the placebo group (*P*=.02). Causative organisms were well balanced between the 2 treatment arms,

Table 2. Baseline Clinical Characteristics Between Treatment Groups

Characteristic	No. of Patients[a]			*P* Value
	Placebo	Corticosteroid	Total	
Affected eye				
Right	122	115	237	.59[b]
Left	128	135	263	
Visual acuity, logMAR, median (25th-75th percentiles)	0.81 (0.38-1.56)	0.84 (0.36-1.70)	0.84 (0.37-1.70)	.33[c]
Visual acuity, Snellen, median (25th-75th percentiles)	20/125 (20/50-20/800)	20/125 (20/50-CF)	20/125 (20/50-CF)	.33[c]
Infiltrate/scar size, median (25th-75th percentiles), mm[d]	2.6 (1.8-3.8)	2.8 (2.1-4.2)	2.7 (1.9-4.1)	.43[c]
Ulcer location				
Entirely in periphery	43	24	67	.004[b]
Partially covering 4-mm circumference	164	156	320	
Completely filling 4-mm circumference	43	68	111	
No photograph	0	2	2	
Hypopyon	136	124	260	.33[b]
Depth				
>0%-33%	115	111	226	.69[b]
>33%-67%	71	80	151	
>67%-100%	64	59	123	
Epithelial defect, median (25th-75th percentiles), mm[d]	2.0 (1.2-3.0)	2.0 (1.3-3.2)	2.0 (1.2-3.1)	.36[c]
Duration of symptoms, median (25th-75th percentiles), d	4 (3-7)	4 (3-7)	4 (3-7)	.88[c]
Ocular surface disease[e]	24	18	42	.42[b]
Dacryostenosis or dacryocystitis	57	46	103	.27[b]
Preexisting corneal abnormalities[f]	10	10	20	>.99[b]
Preexisting eyelid or eyelash abnormalities[g]	4	5	9	>.99[b]
Systemic disease[h]	12	15	27	.69[b]

Abbreviation: CF, counting fingers.
[a] Data expressed as number of patients unless otherwise specified.
[b] Fisher exact test.
[c] Wilcoxon rank sum test.
[d] Geometric mean of the longest diameter and longest perpendicular to that diameter in millimeters.
[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 palsy, eyelid laxity, lagophthalmos, eyelid scars, and madarosis.
[h] Includes diabetes mellitus, asthma, Hansen disease, eczema, psoriasis, human immunodeficiency virus, ichthyosis, hypertension, and malnutrition.

with slightly more *Nocardia* spp and *Pseudomonas aeruginosa* in the corticosteroid group and more *Streptococcus pneumoniae* in the placebo group. However, this difference was not statistically significant (*P*=.77; **Table 3**).

For the primary analysis, a multiple linear regression model revealed that corticosteroids offered no significant improvement compared with placebo (**Table 4**, **Figure 2**) in 3-month BSCVA, controlling for enrollment BSCVA. Sensitivity analyses did not change this finding. At 3 weeks, corticosteroid-treated patients had 0.024 better logMAR acuity (approximately one-fourth of a line), controlling for enrollment BSCVA (95% CI, –0.092 to 0.044; *P*=.49). Multivariate regression models showed that corticosteroid use was not associated with a significantly different infiltrate/scar size at 3 weeks (0.05 mm; 95% CI, –0.09 to 0.15; *P*=.60) or 3 months (0.06 mm; –0.07 to 0.17; *P*=.40). Median time to reepithelialization was 7.0 days (95% CI, 5.5 to 8.5 days) in the placebo arm and 7.5 days (5.5 to 8.5 days; *P*=.25) in the corticosteroid arm. A survival analysis curve adjusting for baseline epithelial defect size found no significant difference in time to reepithelialization in the 2 arms in the first 21 days of the trial (hazards ratio [HR], 0.92; 95% CI, 0.76 to 1.12; *P*=.44). Although more patients in the corticosteroid arm had an epithelial defect at 21 days or

Table 3. Microbiological Culture Results

Organism	No. of Patients[a]		
	Placebo	Corticosteroid	Total
Gram positive	189	177	366
Streptococcus pneumoniae	132	118	250
Nocardia spp	24	32	56
Staphylococcus, coagulase negative	11	11	22
Staphylococcus aureus	10	6	16
Streptococcus viridans group	7	4	11
Corynebacterium spp	3	3	6
Bacillus spp	1	0	1
Mycobacteria spp	0	1	1
Other	1	2	3
Gram negative	64	76	140
Pseudomonas aeruginosa	51	60	111
Moraxella spp	7	8	15
Klebsiella spp	2	1	3
Pseudomonas spp (non-*aeruginosa*)	0	3	3
Enterobacter spp	1	1	2
Haemophilus influenzae	1	0	1
Other	2	3	5
Total[b]	253	253	506

[a] *P*=.77 by the Fisher exact test.
[b] Six patients had a mixed infection.

Table 4. Multiple Linear Regression Predicting 3-Month logMAR BSCVA

Covariate	Coefficient	SE	95% CI	*P* Value
Enrollment BSCVA	0.624	0.031	0.563 to 0.684	<.001
Steroid vs placebo	−0.009	0.039	−0.085 to 0.068	.82

Abbreviation: BSCVA, best spectacle-corrected visual acuity.

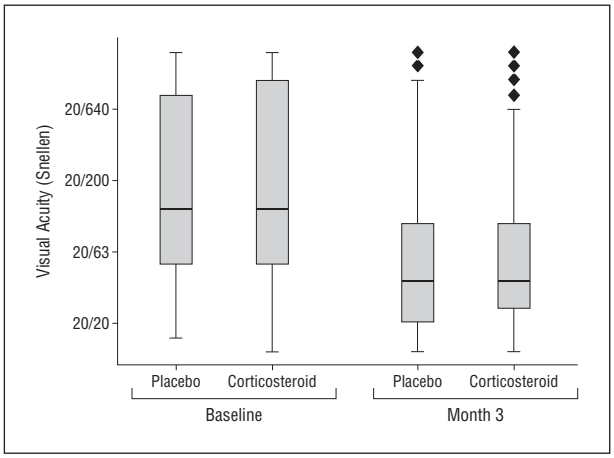

Figure 2. Box plot of baseline and 3-month best spectacle-corrected visual acuity by treatment group. Whiskers extend to the upper and lower adjacent values (largest data point ≤ 75th percentile + [1.5 × interquartile range] and smallest data point ≥ 25th percentile − [1.5 × interquartile range], respectively). Diamonds indicate outliers.

later compared with placebo (44 [17.6%] vs 27 [10.8%]; *P* = .04), a survival analysis assessing healing by 3 months showed no difference between the treatment arms (HR, 0.96; 95% CI, 0.81 to 1.16; *P* = .73).

Adverse events also were compared between the corticosteroid and placebo groups. No significant difference was observed in the number of corneal perforations between treatment arms (*P* > .99; **Table 5**). More patients in the placebo arm developed intraocular pressure (IOP) greater than 25 mm Hg but less than 35 mm Hg (*P* = .04). No IOP elevations above 35 mm Hg were observed in either arm. In 16 patients, the study medication (corticosteroid or placebo) was discontinued: 5 in the corticosteroid arm and 11 in the placebo arm (*P* = .20). Of these patients, 11 had a worsening ulcer or perforation (2 corticosteroid and 9 placebo, *P* = .06), and 5 had growth of fungus on culture and/or smear (3 corticosteroid and 2 placebo, *P* > .99). Sixteen patients discontinued their randomized treatment (placebo or corticosteroid), 11 in the placebo arm and 5 in the corticosteroid arm (*P* = .20). Forty-two changes or additions in antibiotic were observed in the placebo arm and 34 changes or additions in the corticosteroid arm (*P* = .38). Seventeen therapeutic penetrating keratoplasties were performed: 8 in the corticosteroid arm and 9 in the placebo arm (*P* > .99).

Prespecified subgroup analyses looking at the primary outcome (3-month BSCVA) were performed based on baseline BSCVA, ulcer location, infiltrate/scar size, and depth. Subgroup analyses by baseline BSCVA, ulcer location, and infiltrate depth showed a significant effect of corticosteroids (*P* = .03, *P* = .04, and *P* = .04, respectively). In patients with baseline BSCVA of counting fingers or worse, corticosteroid-treated patients had 0.17 better logMAR acuity (approximately 1.7 lines; 95% CI, −0.31 to −0.02; *P* = .03; **Table 6**) compared with placebo at 3 months. In ulcers completely covering the central 4-mm pupil, corticosteroid-treated patients had 0.20 better logMAR acuity (approximately 2 lines; 95% CI, −0.37 to −0.04; *P* = .02) compared with placebo at 3 months. In ulcers with the deepest infiltrates at baseline, corticosteroid-treated patients had 0.15 better logMAR acuity (approximately 1.5 lines; 95% CI, −0.31 to 0.01; *P* = .07) compared with placebo at 3 months; however, this difference was not significant. Subgroup analysis by baseline infiltrate/scar size did not show a significant effect of corticosteroids (*P* = .11). Patients with the largest quartile of infiltrate/scar size at baseline treated with corticosteroids had 0.15 better logMAR acuity (approximately 1.5 lines; 95% CI, −0.31 to 0.01; *P* = .07) compared with placebo at 3 months; however, this difference was not significant.

COMMENT

The SCUT found no significant difference in 3-month BSCVA between patients receiving topical corticosteroid or placebo as adjunctive therapy in the treatment of bacterial corneal ulcers. Before this trial, no conclusive evidence existed regarding the use of corticosteroids for bacterial keratitis. Animal and retrospective studies[14-21] have shown mixed results. Three small, randomized controlled trials were unable to definitively provide evidence regarding the efficacy of corticosteroids as adjunctive therapy in the treatment of bacterial corneal ulcers.[8-10] The use of corticosteroids may increase the duration of infection or increase the risk of recurrent infection.[9,19,20] However, corticosteroids may modulate the immune response, decreasing scarring and improving visual acuity.[11,16,17]

The results of the SCUT demonstrate no obvious benefit in using corticosteroids in the overall study population; also, no apparent serious safety concerns were observed. Noticeably, no apparent increased risk of corneal perforation was incurred with the use of topical corticosteroids. A previous observational study[22] has suggested that the use of corticosteroids is a risk factor for requiring penetrating keratoplasties in microbial keratitis. In our trial, no difference was observed in the number of penetrating keratoplasties in the corticosteroid or placebo arm, suggesting that the use of corticosteroids is not a major concern for the risk of perforation or the need for a therapeutic penetrating keratoplasties. Also, the use of corticosteroids with our treatment regimen was not associated with an increase in IOP. In fact, more patients had elevated IOP in the placebo arm than in the corticosteroid arm.

Table 5. Adverse Events by Treatment Group

Adverse Event[a]	No. of Patients			*P* Value[b]
	Placebo	Corticosteroid	Total	
Serious	13	15	28	.85
Corneal perforation	8	7	15	
Endophthalmitis	0	0	0	>.99
IOP >35 mm Hg	0	0	0	
Death	5	7	12	.77
Systemic infection	0	1	1	>.99
Myocardial infarction or stroke	0	0	0	
Other	0	0	0	
Nonserious	34	40	74	.53
Local allergic reaction	0	0	0	>.99
Increase in hypopyon	4	4	8	>.99
Increase in infiltrate size >50%	4	9	13	.26
No healing of epithelial defect by 21 d	27	44	71	.04
IOP elevated >25 mm Hg but <35 mm Hg	10	2	12	.04
Progressive corneal thinning	2	0	2	.50
Other	13	9	22	.51

Abbreviation: IOP, intraocular pressure.
[a] Patients may have had more than 1 such event.
[b] Fisher exact test.

Table 6. Prespecified Subgroup Analyses Predicting 3-Month logMAR BSCVA[a]

Baseline Subgroup	No.	Mean Placebo	Mean Corticosteroid	Coefficient (95% CI)	*P* Value
Baseline BSCVA subgroups, logMAR					
<20/40	90	−0.02	0.06	0.08 (−0.08 to 0.25)	.33
20/40 to 20/800	235	0.38	0.36	0.01 (−0.09 to 0.11)	.85
CF or worse	117	1.15	1.00	−0.17 (−0.31 to −0.02)	.03
Test for linear trend	. . .	. . .	. . .	. . .	.03
Ulcer location subgroups					
Entirely in periphery	60	0.13	0.09	0.01 (−0.20 to 0.22)	.90
Partially covering central 4-mm circumference	283	0.39	0.40	0.04 (−0.05 to 0.14)	.38
Completely filling central 4-mm circumference	97	1.08	0.89	−0.20 (−0.37 to −0.04)	.02
Interaction	. . .	. . .	. . .	. . .	.04
Infiltrate depth subgroups					
>0%-33%	207	0.26	0.35	0.06 (−0.05 to 0.17)	.31
>33%-67%	135	0.47	0.52	0.01 (−0.13 to 0.14)	.94
>67%-100%	100	0.86	0.80	−0.15 (−0.31 to 0.01)	.07
Test for linear trend	. . .	. . .	. . .	. . .	.04
Infiltrate/scar size geometric mean, mm					
0-1.90	113	0.19	0.18	0.05 (−0.10 to 0.20)	.53
1.91-2.70	111	0.29	0.39	0 (−0.15 to 0.16)	.95
2.71-4.06	114	0.53	0.53	0.03 (−0.12 to 0.18	.70
4.07-8.90	104	0.96	0.85	−0.15 (−0.31 to 0.01)	.07
Test for linear trend	. . .	. . .	. . .	. . .	.11

Abbreviations: BSCVA, best spectacle-corrected visual acuity; CF, counting fingers; ellipses, not applicable.
[a] Multiple linear regression.

Some ophthalmologists are concerned that corticosteroids may delay healing of the epithelial defect; a pilot study[9] preceding this trial showed significantly delayed reepithelialization in corticosteroid-treated patients. In the current study, the survival analysis, which did not show a difference in epithelial defect healing, controlled for baseline epithelial defect size and was censored at 21 days from enrollment. Of the patients who had an epithelial defect at 21 days or later after enrollment, a higher proportion was observed in the corticosteroid arm compared with the placebo arm, but this difference did not adjust for baseline characteristics. By 3 months, no difference was observed in the rates of healing between patients with ulcers receiving corticosteroid drops vs placebo.

An intriguing finding of the study was that prespecified subgroup analyses demonstrated a benefit in 3-month visual acuity using corticosteroids in ulcers with greatest severity at presentation. Corticosteroid treatment was associated with a benefit in visual acuity compared with the placebo group in the subgroups with the worst visual acuity and central ulcer location at baseline. These subgroup analyses suggest that patients with severe ulcers, who have the most to gain in terms of visual acu-

ity, may benefit from the use of corticosteroids as adjunctive therapy. Of interest, physicians may most fear using corticosteroids in these patients.

The treatment arms were well balanced for most baseline characteristics. Ulcer location was the only baseline characteristic that was significantly different across the 2 treatment arms. More patients in the corticosteroid arm had an ulcer that completely filled the central 4-mm pupil; more patients in the placebo arm had an ulcer that partially covered the pupil. Ulcers that were completely covering the 4-mm pupil were larger than those partially covering it or existing entirely in the periphery; the former type yielded worse visual acuity. However, because we controlled for baseline visual acuity and baseline infiltrate/scar size in our analyses, it is unlikely that differences in the location of the ulcer at baseline significantly biased the results of the trial.

This study had a large sample size and had a lower loss-to-follow-up rate than planned for in calculation of the sample size. As a result, this study had the power to detect a relatively small effect size of a 1-line difference in visual acuity between the 2 groups. Despite this power, we did not detect a difference in 3-month visual acuity overall between the 2 groups. Because of the balance between the 2 groups and the randomized controlled method of the trial, if a difference exists in 3-month BSCVA with the use of corticosteroids overall, it is likely small. However, a differential effect of corticosteroids may exist in subgroups of corneal ulcers, as described herein in the prespecified subgroup analyses. We plan to continue to conduct subgroup analyses to further explore a potential benefit of corticosteroid treatment, including in subgroups by organism, antibiotic susceptibility, and other clinical or demographic factors.

This study has several potential limitations. Generalizability can be an issue when patients are enrolled in diverse environments. Despite the fact that most ulcers in this trial occurred in non–contact lens wearing individuals enrolled in India, we believe that the results of this trial are relevant to a large population. Baseline characteristics, such as infiltrate/scar size and BSCVA, were comparable or slightly worse than those reported in previous studies[23-25] of microbial keratitis. The most common organisms reported also have been commonly reported in the United States and Europe, including *S pneumoniae* and *P aeruginosa*.[23,26-29] *Nocardia* spp, which is rarely reported in the United States and Europe, was the third most commonly isolated organism in this trial. Although the distribution of organisms was different between the United States and India, all 5 bacteria isolated from ulcers in the United States could be found in the top 8 most common bacterial isolates from ulcers in India.

The treatment regimen selected also could have an effect on outcomes. Because of the pretrial concerns regarding corticosteroids and adverse events, such as perforation, some investigators were reluctant to proceed with a more aggressive regimen. However, it is possible that an increased frequency or duration of corticosteroid use could have a larger effect. To isolate the difference between use of corticosteroid and placebo, the antibiotic was standardized. We selected a broad-spectrum fluoroquinolone commonly used in practice,[30] which may not have been the most efficacious for each patient. Physicians were allowed to change or add antibiotics at any time if they thought it was medically necessary. The rate of antibiotic change was approximately 15% in both arms of the trial. We plan to conduct analyses using SCUT data to evaluate the role of susceptibility and clinical outcomes. In our pilot study,[31] minimum inhibitory concentration was significantly associated with larger infiltrate/scar size at 3 months.

In conclusion, the SCUT found no overall difference in 3-month visual acuity with the use of topical corticosteroids as adjunctive therapy for bacterial keratitis compared with placebo. Also, there were no major safety concerns with their use. Prespecified subgroup analyses suggest that there may be a role for topical corticosteroids in ulcers that are more severe at baseline. However, a larger study examining only severe corneal ulcers is needed to confirm this supposition. To our knowledge, this is the first large randomized controlled trial to provide evidence regarding the safety and efficacy of the use of corticosteroids in the treatment of bacterial corneal ulcers.

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