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Visual recovery in treated bacterial keratitis

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Abstract

Bacterial keratitis is a leading cause of visual impairment worldwide. However, the natural history of treated bacterial keratitis has not been well characterized. We performed a secondary analysis of the Steroids for Corneal Ulcers Trial (SCUT; clinicaltrials.gov #NCT00324168) to better characterize the rate of visual acuity improvement after successful antimicrobial treatment.

Keywords

prospective; visual acuity; outcomes; keratitis; clinical trial

Methods

SCUT was a randomized clinical trial conducted from 2006–2010 in the United States and India. The trial received ethical approval from Aravind Eye Hospital, Dartmouth-Hitchcock

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Medical Center, and the University of California, San Francisco. The methods of the trial have been described previously.[1] Patients with culture-proven bacterial keratitis who had been treated with ≥48 hours of topical moxifloxacin were randomized to topical prednisolone phosphate or topical placebo. Certified refractionists assessed logarithm of the minimum angle of resolution (logMAR) best spectacle corrected visual acuity (BSCVA) with a Tumbling "E" chart at enrollment, 3 weeks (study window: 2.5–5 weeks), 3 months (window: 2.5–5 months), and 12 months (window: 10–14 months). Study participants with counting fingers, hand motions, light perception, or no light perception visual acuity were assigned a logMAR of 1.7, 1.8, 1.9, or 2.0, respectively.

Results

Of 500 study participants enrolled in SCUT, 375 (75%) had visual acuity assessed within the time window for all follow-up visits. Individuals who were lost to follow-up were generally older and had worse vision compared with those who were not lost to follow-up (Table 1, available at http://aaojournal.org).

BSCVA improved over the 12 months of the study for the vast majority of study participants (Table 2, available at http://aaojournal.org). Results were similar in a sensitivity analysis in which missing values were imputed, with the exception that study participants with the worst vision at enrollment had slightly less improvement (Table 2).

Six study participants had cataract extraction, 8 had penetrating keratoplasty, and 1 had cataract extraction and penetrating keratoplasty. Visual recovery was generally suboptimal for these patients: among the 9 participants who underwent penetrating keratoplasty, the median 12-month BSCVA was 1.7 logMAR units (Counting Fingers; interquartile range [IQR] 1.7 to 1.8).

We restricted the remaining analyses to the 360 study participants who did not have intraocular surgery. Visual acuity among these non-operated individuals improved significantly over each time interval, with a median improvement of 2.4 (IQR 0.4 to 5.5) logMAR lines from enrollment to 3 weeks, 0.8 (IQR 0 to 2.2) lines from 3 weeks to 3 months, and 0.2 (IQR −0.4 to 1.0) lines from 3 months to 12 months ($P<0.001$ for each interval, Wilcoxon signed-rank test).

Similar analyses stratified by pre-specified clinical characteristics at enrollment (visual acuity, infiltrate size, infiltrate depth, ulcer location, organism, and country) are shown in Table 3 (available at http://aaojournal.org). In general, BSCVA improvement was more pronounced for the most severe of each of these strata. For example, participants with BSCVA better than 20/40 at enrollment had a median of 1.2 (IQR 0.2 to 2.2) lines of improvement during the 12 months of the study, compared to 4.8 (IQR 2.8 to 7.2) lines for the subgroup with enrollment BSCVA of 20/40–20/800 and 11.4 (IQR 3.8 to 13.4) lines for the CF-or-worse subgroup. Most strata had significant improvement in visual acuity from enrollment to 3 weeks and from 3 weeks to 3 months, but only the most severe strata experienced BSCVA improvement from 3 months to 12 months.

In a multivariate linear regression including all the enrollment characteristics in Table 3, only enrollment BSCVA was a significant predictor of visual improvement from enrollment to 12 months: compared to participants with BSCVA >20/40, the 20/40–20/800 subgroup experienced 3.0 (95%CI 1.8 to 4.2) lines of improvement and the CF-or-worse subgroup experienced 6.4 (95%CI 4.8 to 8.0) lines of improvement ($P<0.001$).

The comparison of topical corticosteroids versus placebo at 3 months and 12 months is described elsewhere.[2, 3]

Discussion

Few studies have prospectively followed patients with infectious keratitis to monitor change in visual acuity. In a prospective study of 273 individuals with presumed infectious keratitis in Nepal, 52.7% experienced ≥2 lines improvement in pinhole visual acuity.[4] A study of 30 patients with culture-proven bacterial keratitis found an average visual acuity improvement of 2.5 lines by 10 weeks.[5] Our results are consistent with these reports: in the current study, half of patients achieved a 3.8 line improvement in visual acuity by 3 months, although the degree of improvement was associated with the severity of the corneal ulcer at enrollment.

We found that enrollment visual acuity was the most significant predictor of visual acuity improvement at 12 months. These results may be helpful when counseling patients with bacterial keratitis. On average, patients with mild vision loss (better than 20/40) can expect about 1 line of improvement, with continuous improvement until 3 months. Patients with moderate vision loss (20/40 to 20/800) can expect a rapid improvement in vision over the first 3 weeks and a cumulative 4- to 5-line improvement by 3 months, but then little improvement thereafter. Patients with severe vision loss (CF or worse) can expect a marked improvement in vision over the subsequent 12-month period (approximately 11 lines), and can even expect 1 line of this improvement to occur after 3 months.

This study's strengths are its large sample size, 12 months of follow-up, and standardized assessment of BSCVA at pre-specified time points. Its main weakness is that it is generalizable only to patients who would be eligible for SCUT and remained in follow-up for all 3 study visits. Although the results of this study may therefore be biased towards those with better outcomes, our sensitivity analysis using imputed BSCVA suggests this was not the case. The vast majority of study participants were enrolled in India. Although this may limit generalizability, we were unable to detect any large differences in visual acuity improvement between the Indian and American sites.

In conclusion, persons with bacterial keratitis experienced marked improvement in visual acuity in the first 3 months after starting treatment, and experienced a smaller but still significant improvement in vision from 3 to 12 months after starting treatment. Improvement in visual acuity was greatest for those study participants with the most severe ulcers at enrollment.

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Table 1

Characteristics of study participants with complete and incomplete follow-up

Enrollment characteristic	Incomplete Follow-up N=125	Complete Follow-up N=375	*P*-value*
Female sex	57 (45.6%)	170 (45.3%)	0.96
Age, median (IQR), years	55 (45 to 65)	52 (40 to 60)	0.01
Enrollment site			0.17
India	119 (95.2%)	366 (97.6%)	
United States	6 (4.8%)	9 (2.4%)	
Visual acuity, logMAR, median (IQR)	1.08 (0.46 to 1.7)	0.74 (0.34 to 1.7)	0.01
Visual acuity subgroup			0.02
>20/40	17 (13.6%)	80 (21.3%)	
20/40 to 20/800	66 (52.8%)	200 (53.3%)	
CF or worse	42 (33.6%)	95 (25.3%)	
Location			0.16
Completely filling central 4 mm	13 (10.4%)	54 (14.4%)	
Partially covering central 4 mm	79 (63.2%)	241 (64.3%)	
Entirely peripheral	32 (25.6%)	79 (21.1%)	
Missing data	1 (0.80%)	1 (0.3%)	
Infiltrate depth in corneal stroma			0.31
<33%	63 (50.4%)	163 (43.5%)	
>33–67%	32 (25.6%)	119 (31.7%)	
>67%	30 (24.0%)	93 (24.8%)	
Infiltrate size geometric mean, mm			0.27
0–1.90	30 (24.0%)	96 (25.6%)	
1.91–2.70	28 (22.4%)	97 (25.9%)	
2.71–4.06	30 (24.0%)	94 (25.1%)	
4.07–8.90	37 (29.6%)	88 (23.5%)	
Causative organism			0.19
Streptococcus pneumoniae	70 (56.0%)	178 (47.5%)	
Pseudomonas aeruginosa	25 (20.0%)	85 (22.7%)	
Nocardia species	7 (5.6%)	48 (12.8%)	
Moraxella species	6 (4.8%)	8 (2.1%)	
Other	17 (13.6%)	56 (14.9%)	
Treatment Assignment			0.61
Corticosteroid	60 (48.0%)	190 (50.7%)	
Placebo	65 (52.0%)	185 (49.3%)	

IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; CF = Counting Fingers Values indicate numbers (proportion) unless otherwise noted.

*Kruskal-Wallis test or Wilcoxon rank sum test

Table 2

Distribution of 12-month best spectacle corrected visual acuity in the Steroids for Corneal Ulcers Trial (SCUT), stratified by visual acuity at enrollment

Month 12 Visual Acuity	Enrollment Visual Acuity			
	Better than 20/40	**20/40 to >20/200**	**20/200 to 20/800**	**CF or worse**
Complete Case	*N*=80	*N*=141	*N*=58	*N*=96
Better than 20/40	79 (98.8%)	97 (68.8%)	17 (29.3%)	20 (20.8%)
20/40 to >20/200	0 (0%)	43 (30.5%)	32 (55.2%)	47 (49.0%)
20/200 to 20/800	0 (0%)	0 (0%)	3 (5.2%)	7 (7.3%)
CF or worse	1 (1.3%)	1 (0.7%)	6 (10.3%)	22 (22.9%)
Imputed Data	*N*=97	*N*=182	*N*=83	*N*=138
Better than 20/40	96 (99.0%)	127 (69.8%)	21 (25.3%)	23 (16.7%)
20/40 to >20/200	0 (0%)	52 (28.6%)	52 (62.7%)	65 (47.1%)
20/200 to 20/800	0 (0%)	1 (0.6%)	4 (4.8%)	21 (15.2%)
CF or worse	1 (1.0%)	2 (1.1%)	6 (7.2%)	29 (21.0%)

CF = Counting Fingers. Complete case data refer to the 375 study participants with best spectacle corrected visual acuity (BSCVA) at enrollment, 3 weeks, 3 months, and 12 months. Imputed data refer to all 500 study participants, using imputed visual acuity measurements for missing 12-month BSCVA (deterministic imputation using iterative linear regressions for the missing 3-week, 3-month, and 12-month values; regression models included the BSCVA at the previous visit and time elapsed since the previous visit).

Table 3

Improvement in lines of best spectacle corrected visual acuity during each study interval for study participants not undergoing surgery during the study period, stratified by pre-specified enrollment characteristics

		logMAR lines of BSCVA improvement		
Enrollment characteristic	**N***	**Enrollment to 3 weeks**	**3 weeks to 3 months**	**3 months to 12 months**
Visual Acuity				
>20/40	79	**0.6 (0 to 1.4)**	**0.4 (−0.2 to 1.2)**	0 (−0.4 to 0.4)
20/40 to 20/800	191	**3.0 (1.2 to 5.6)**	**1.0 (0.2 to 2.0)**	0.2 (−0.4 to 0.8)
CF or worse	90	**3.6 (0 to 10.2)**	**1.5 (0 to 4.8)**	**1.0 (0 to 3.0)**
Test for trend		<0.001	<0.001	<0.001
Ulcer location				
Entirely in periphery	51	**0.8 (0 to 1.8)**	0.2 (−0.2 to 0.8)	−0.2 (−0.6 to 0.2)
Central 4mm-partial	234	**2.6 (0.6 to 5.4)**	**0.8 (0 to 2.0)**	0.1 (−0.4 to 0.8)
Central 4mm-complete	74	**3.3 (1.0 to 7.8)**	**2.0 (0 to 4.6)**	**0.9 (0 to 3.0)**
Test for trend		<0.001	<0.001	<0.001
Infiltrate depth				
≤33%	170	**1.8 (0.4 to 4.4)**	**0.6 (0 to 1.8)**	0 (−0.4 to 0.6)
>33%–67%	111	**3.0 (1.0 to 5.8)**	**1.0 (0 to 2.2)**	0.2 (−0.4 to 1.0)
>67%	79	**2.6 (0 to 7.8)**	**1.4 (0 to 4.6)**	**0.4 (−0.4 to 2.0)**
Test for trend		0.19	0.002	0.003
Infiltrate/scar size				
0–1.90	91	**1.6 (0.6 to 3.2)**	**0.4 (−0.2 to 1.2)**	0 (−0.8 to 0.4)
1.91–2.70	96	**1.7 (0.4 to 4.2)**	**0.8 (0 to 1.5)**	0 (−0.4 to 0.8)
2.71–4.06	90	**3.3 (0.6 to 6.8)**	**1.3 (0.4 to 3.0)**	0.2 (−0.4 to 1.0)
4.07–8.90	83	**3.0 (0 to 7.8)**	**2.0 (0 to 5.0)**	**1.0 (0 to 2.8)**
Test for trend		0.01	<0.001	<0.001
Causative organism				
S. pneumoniae	171	**2.6 (0.6 to 5.6)**	**0.8 (0 to 2.0)**	0.2 (−0.4 to 1.2)
P. aeruginosa	83	**3.2 (0.6 to 8.4)**	**1.4 (0.2 to 3.0)**	0.2 (−0.6 to 1.4)
Nocardia species	46	0.6 (−0.4 to 1.8)	0.6 (−0.2 to 1.8)	0.2 (0 to 1.0)
Moraxella species	7	4.6 (1.4 to 6.4)	0.6 (0.4 to 3.6)	0 (−1.2 to 0.4)
Others	53	**1.8 (0.4 to 3.4)**	**0.6 (0 to 1.6)**	0 (−0.6 to 0.4)
Kruskal-Wallis test		<0.001	0.05	0.10
Country				
United States	9	4.2 (2.2 to 4.8)	0.6 (0.2 to 2.2)	0.4 (0 to 0.6)
India	351	**2.2 (0.4 to 5.6)**	**0.8 (0 to 2.2)**	**0.2 (−0.4 to 1.0)**
Kruskal-Wallis test		0.40	0.97	0.49

CF = Counting Fingers

Values indicate median change in lines of logMAR best spectacle corrected visual acuity (BSCVA) during time interval, with interquartile range. Positive values indicate improvement in vision. Values in bold indicate $P<0.001$ in a Wilcoxon signed rank test comparing the BSCVA at the subsequent time points. Differences between the levels of a stratum were assessed with the nonparametric test for trend for ordinal variables and the Kruskal-Wallis test for nominal variables. To account for the problem of multiple comparisons, a P-value<0.001 was considered significant for all analyses in this report.

* Number in each subgroup at enrollment