Double-masked, sham and placebo-controlled trial of corneal cross-linking and topical difluprednate in the treatment of bacterial keratitis: Steroids and Cross-linking for Ulcer Treatment Trial (SCUT II) study protocol

Naveen Radhakrishnan,1 Venkatesh N Prajna,2 Lalitha S Prajna,3 Anitha Venugopal,2 Shivanandha Narayana,4 Revathi Rajaraman,5 Guillermo Amescua,6 Travis C Porco,7,8 Thomas M Lietman,9 Jennifer Rose-Nussbaumer10

ABSTRACT

Introduction Although antibiotics are successful at achieving microbiological cure in infectious keratitis, outcomes are often poor due to corneal scarring. Ideal treatment of corneal ulcers would address both the infection and the inflammation. Adjunctive topical steroid treatment may improve outcomes by reducing inflammation. Corneal cross-linking (CXL) is a novel prospective therapy that may simultaneously reduce both inflammatory cells and bacterial pathogens. The purpose of this study is to determine differences in 6-month visual acuity between standard medical therapy with antibiotics versus antibiotics with adjunctive early topical steroid therapy versus antibiotic treatment plus CXL and early topical steroids.

Methods and analysis This international, randomised, sham and placebo-controlled, three-arm clinical trial randomises patients with smear positive bacterial ulcers in a 1:1:1 fashion to one of three treatment arms: (1) topical 0.5% moxifloxacin plus topical placebo plus sham CXL; (2) topical 0.5% moxifloxacin plus diffuprednate 0.05% plus sham CXL; or (3) the CXL group: topical 0.5% moxifloxacin plus diffuprednate 0.05% plus CXL.

Ethics and dissemination We anticipate that both adjunctive topical steroids and CXL will improved best spectacle corrected visual acuity and also reduce complications such as corneal perforation and the need for therapeutic penetrating keratoplasty. This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. Our results will be disseminated via ClinicalTrials.gov website, meetings and journal publications. Our data will also be available on reasonable request.

Trial registration number NCT04097730.

BACKGROUND

Although antibiotics are successful at achieving microbiological cure in infectious keratitis, outcomes are often poor due to corneal scarring. Randomised trials comparing different antibiotic treatments have not been able to demonstrate superiority of one antibiotic over another.1 During acute infection pathogens, keratocytes and other inflammatory cells secrete enzymes that promote protein degradation and keratolysis with resultant opacity and irregular astigmatism. Corneal perforation can also result, however, subgroup analyses suggested that earlier steroid treatment of large, central, non-Nocardia ulcers led to better clinical outcomes.3 6 These subgroup analyses have led some to conclude that topical corticosteroids may be beneficial for specific subgroups of culture-positive bacterial ulcers and that they were most effective when administered early with appropriate antibiotics.5 6

Corneal cross-linking (CXL) is a novel prospective therapy that may simultaneously reduce both inflammatory cells and bacterial pathogens.5 9 Ultraviolet A (UV-A) + riboflavin
is effective in vitro against common bacterial ocular pathogens, such as *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*. Multiple case reports have suggested potential benefits of CXL with riboflavin (UVX) for treatment of bacterial keratitis, including resolution of resistant infection, halting of progressive melting and symptomatic improvement. In one small case series, bacterial infections resolved even though patients were treated exclusively with photochemically activated riboflavin. Therapies to reduce inflammation may improve outcomes; however, there are concerns about potentiating infection and poor healing. The possibility that UVX may immediately reduce the burden of infectious organisms makes subsequent anti-inflammatory treatment safer. Here, we describe a three-arm randomised controlled clinical trial to investigate CXL and early topical steroids as adjuvant therapies in the treatment of bacterial corneal ulcers.

### Methods/Design

#### Study design

The Steroids and Cross-linking for Ulcer Treatment Trial II (SCUT II) is an international, randomised, sham and placebo-controlled, three-arm clinical trial (full protocol available in online supplemental file 1). The purpose of this study is to determine differences in 6-month visual acuity between standard therapy with antibiotics versus early antibiotics with adjuvant steroid versus antibiotic treatment plus CXL and early steroids. Patients presenting to one of the Aravind Eye Hospitals in India, University of California, San Francisco, Kaiser Permanente Northern California, or Bascom Palmer Eye Institute at the University of Miami with smear and/or culture-positive non-*Nocardia* bacterial corneal ulcers and moderate vision loss, defined as Snellen visual acuity of 20/40 or worse and corneal thickness of greater than or equal to 350 µm as measured on anterior segment optical coherence tomography (AS-OCT), will be included. Figure 1 provides a schematic outline of the study.

Those who agree to participate will be randomised in a 1:1:1 fashion to one of three treatment arms:

- **Group 1:** standard therapy group, topical 0.5% moxifloxacin plus topical placebo plus sham CXL.
- **Group 2:** early steroids group, topical 0.5% moxifloxacin plus difluprednate 0.05% plus sham CXL.
- **Group 3:** CXL group, topical 0.5% moxifloxacin plus difluprednate 0.05% plus CXL.

#### Objective and hypothesis

The objectives of this study are (1) to determine if CXL is a beneficial adjuvant in the treatment of smear-positive bacterial ulcers; (2) to determine if early topical steroids are a beneficial adjuvant in the treatment of smear-positive bacterial ulcers; and (3) to determine which ulcer characteristics predict the most benefit from the addition of adjuvant CXL and/or early steroids. We anticipate that CXL will result in better best spectacle corrected visual acuity (BSCVA) at 6 months compared with antibiotic alone. We hypothesise that those randomised to early topical steroids will have improved BSCVA at 6 months compared with antibiotic alone. We hypothesise that large central bacterial ulcers will benefit most from adjuvant early topical steroids and/or CXL.

#### Study oversight

An independent Data and Safety Monitoring Committee (DSMC) oversees the data collection and safety of the study. The DSMC members have expertise in ophthalmology with cornea subspecialty training, biostatistics and ethics. Interim reports for the DSMC are prepared by the Data Coordinating Center at Proctor. These reports include (1) recruitment overall and by study site, (2) compliance and (3) retention. The reports also list study outcomes, including 6-month BSCVA and microbiological outcomes, and all adverse outcomes, including mortality and perforations. The DSMC meets annually in person and biannually via teleconference to monitor study progress and safety. There are also ad hoc meetings as needed. Study investigators conduct site visits at least triannually. The principal investigators notify the DSMC, study sites and institutional review boards of any changes to study protocols or any deviations from the trial protocols.

#### Setting

Participants will be enrolled at seven sites in India and the USA. In India, participants will be enrolled at Aravind Eye Hospitals in the cornea clinic in Coimbatore, Madurai, Pondicherry and Tirunelveli. In the USA, participants will be enrolled at the Proctor Foundation clinic at the University of California, San Francisco in San Francisco, California, at Bascom Palmer Eye Institute at the University of Miami in Miami, Florida, and at Kaiser Permanente Northern California medical facilities in Oakland.

#### Inclusion and exclusion criteria

Inclusion criteria include age older than 18, presence of smear and/or culture-positive typical bacterial keratitis (ie, non-*Nocardia* or *Mycobacteria*) and Snellen visual acuity of 20/40 or worse with a central corneal thickness greater than or equal to 350 µm as measured by AS-OCT. Exclusion criteria include evidence of concurrent viral, fungal, *Acanthamoeba* or atypical bacterial keratitis, impending or frank corneal perforation, involvement of the sclera, non-infectious or autoimmune keratitis, history of recent intraocular surgery or prior corneal transplant, and fellow eye visual acuity worse than 20/200. The investigator will confirm their ability to understand the study and willingness to participate.

#### Randomisation

Each study eye is randomly assigned to the treatment group. Block randomisation was performed using a computer program (R statistical package V.2.12; R Foundation for Statistical Computing, Vienna, Austria) by the coordinating site. Once an eye is enrolled in the study, the study coordinator will assign the study participant’s eye...
an identification (ID) (alphanumeric code) and topical moxifloxacin 0.5% will begin every hour for 2 days and then every 2 hours while awake until resolution of the epithelial defect. The study coordinator will organise the procedure in the operating room within 48 hours. Once the study participant has been assigned a study participant ID and randomised to treatment group, they will be included in the intent-to-treat analysis.

**Intervention and masking: cross-linking**

Study participants will undergo CXL with a modified Dresden protocol or sham CXL within 48 hours of enrolment. For the modified Dresden protocol, patients will not have an 8 mm epithelial debridement, rather only the epithelium over the infiltrate will be debridged.

All participants will receive a 30 min loading dose of topical 0.1% riboflavin and 20% dextran T500 drops every 2 min. Full penetration through the cornea with anterior segment flare will be confirmed prior to CXL procedure. This will be followed by exposure to continuous UV-A light at a wavelength of 365 nm with an irradiance of 3 mW/cm² for 30 min and a total dose of 5.4 J/cm² (UV lamp; Avedro KXL System, Waltham, Massachusetts, USA for USA) for those randomised to CXL. During irradiation patients will continue to receive topical riboflavin

**Figure 1** Enrolment schema for the Steroids and Cross-linking for Ulcer Treatment Trial. AS-OCT, anterior segment optical coherence tomography; BSCVA, best spectacle corrected visual acuity; CXL, corneal cross-linking; VFQ, Visual Function Questionnaire.
at 5 min intervals. Sham CXL simulates this experience; however, a blue penlight will be shined adjacent to the patient, carefully avoiding exposure to the cornea, and the cornea will be covered with a corneal light shield. In place of riboflavin we will use either saline drops or saline drops dyed with fluorescein. Riboflavin will not be used in the sham procedure due to concern that photochemical activation of the riboflavin may occur with exposure to ambient light and therefore produce some treatment effect. All study participants will have repeat corneal cultures 30 min after the CXL or sham CXL procedure.

Due to the nature of the surgical intervention, the surgeon and the technician performing cross-linking will not be masked. The patient, the physician performing repeat scraping and clinical follow-up, the microbiologist, and the refractionist performing the BSCVA will be masked to treatment arm.

**Intervention and masking: difluprednate**

Commercially available difluprednate will be repackaged into the same bottles as placebo by a compounding pharmacy (Rancho Park, Los Angeles, California). Placebo will be labelled identically to ensure adequate masking of study physicians and patients.

**Data collection and management**

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data reported. Table 1 outlines the schedule of enrolment, interventions and assessments.

Clinical data (including adverse events, concomitant medications and expected adverse reactions data) and clinical laboratory data will be entered into Research Electronic Data Capture (REDCap), a 21 CFR Part 11-compliant data capture system provided by the Data Coordinating Center at the University of California, San Francisco. These data will be kept confidential. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete or inaccurate.

### Table 1 Schedule of enrolment, interventions and assessments for the Steroids and Cross-linking for Ulcer Treatment Trial

| Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 |
|---------|---------|---------|---------|---------|---------|---------|---------|
| Day 0   | Day 1   | Day 2   | Day 3   | 3-week follow-up | 3-month follow-up | 6-month follow-up | 12-month follow-up |

**Enrolment**

- Consent and authorisation X
- Baseline form X
- Clinical drawing X X X X X
- VFQ X
- Follow-up form X X X X X
- Final form X

**Interventions**

- CXL/sham CXL X
- Study medication* X

**Assessments**

- IOP X X X X X X
- Pain scale X X X
- AS-OCT X X X X X
- Confocal microscopy X X X X X
- Pentacam topography X X X X X
- Clinical photography† X X X X X
- Slit lamp examination X X X X X X
- BSCVA/ETDRS/MRx X X X X X
- Pinhole visual acuity X
- Culture/smear X X

**Total visit time**

- 2 hours 2 hours 3 hours 0.5 hours 1 hour 1 hour 1 hour 1 hour

*Difluprednate versus placebo starting at 24 hours.
†Clinical photographs also taken on adverse events.

AS-OCT, anterior segment optical coherence tomography; BSCVA, best spectacle-corrected visual acuity; BSCVA, best spectacle corrected visual acuity; CXL, corneal cross-linking; ETDRS, early treatment diabetic retinopathy study; MRx, manifest refraction; VFQ, visual function questionnaire.
Primary outcome measurement and statistical analyses

Visual acuity

The primary outcome will be 6-month BSCVA. We will use multiple linear regression models to evaluate BSCVA measured with covariates for treatment arm (expressed as a categorical variable for randomisation group), study site (randomisation strata) and baseline pinhole visual acuity.

Secondary outcome measures and statistical analyses

Visual acuity

As secondary analyses we will also look at 3-week, 3-month and 12-month BSCVA. We will use multiple linear regression models to evaluate BSCVA measured with covariates for treatment arm (expressed as a categorical variable for the randomisation group), study site (randomisation strata) and baseline pinhole visual acuity.

Microbiological cure

Studies have suggested that, in addition to providing an initial diagnosis, repeated culture can be used to assess response to treatment and is highly correlated with clinical outcomes such as visual acuity. We will reculture all study participants on day 2 to assess the effect of CXL on the rate of microbiological cure. We hypothesise that those in the CXL group (group 3) will have a higher rate of microbiological cure on day 2 cultures than those randomised to the standard therapy (group 1) or early steroid group (group 2). Participants in both groups 1 and 2 will serve as the comparison group, increasing the power in this analysis.

We propose the primary analysis to be a Fisher’s exact test comparing the proportion of positivity at follow-up between initially culture-positive individuals who were assigned to cross-linking (group 3) versus initially culture-positive individuals assigned to sham cross-linking (groups 1 and 2). Additionally, we will report the results for initially culture-negative individuals as a supplementary analysis in a logistic regression with assignment, indicators for site (randomisation strata) and initial culture results as covariates.

Scar/infiltrate

The analysis for scar/infiltrate size will follow the templates for visual acuity given above. Multiple linear regression models will be used to evaluate 12-month scar size by treatment arm (a three-level categorical variable) while correcting for baseline measurements. As in the primary analysis, we will perform pairwise comparisons between arms with a significance level of 0.05/2=0.025. Corneal thinning and scarring will be evaluated similarly using AS-OCT, correcting for baseline values.

Visual Function Questionnaire

The Visual Function Questionnaire (VFQ) will be compared between the three groups controlling for day 1 VFQ: National Eye Institute (NEI-VFQ) in the USA and Indian (IND-VFQ in India. This will be conducted using linear regression with baseline and assignment variables.
enrolment was 0.216. We thus assumed a residual SD of 0.293/√(1 − 0.216^2) = 0.286.

Assuming a significance level of 0.05/2=0.025, and allowing for approximately 15% loss to follow-up, we estimate that we will have 80% power to detect a 1.4-line difference (Log of minimum angle of resolution [logMAR] 0.14) between groups with 93 study participants per arm (279 total). This calculation applies to each of the two prespecified primary outcomes for this trial (corresponding to the two separate research questions) and is based on the standard power formula for the t-test (using an estimated residual SD). Note that if the trial were to enrol 60 patients per arm, the minimum detectable effect under all the same assumptions would be 1.8 lines (logMAR 0.18).

**Dissemination plan**

This study will comply with the National Institute of Health (NIH) Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial is registered at ClinicalTrials.gov, and the results from this trial will be submitted and published on ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals and to present these data at national and international meetings. Consistent with the collaborative nature of the proposed research, the Principal Investigator anticipates sharing all data generated by the study with collaborators. Analytical data sets that will be developed through the project will comply with the NIH Data Sharing Policy. The analytical data sets from this project will include patient-level data generated from the study visits. Data from the trial will be made available on reasonable request.

**DISCUSSION**

Infectious keratitis is a leading cause of monocular blindness worldwide. In the USA, bacteria are the most common etiology for corneal ulcers, and they are often associated with contact lens use. Despite appropriate antibiotic treatment, severe cases can progress rapidly and cause permanent vision loss requiring corneal transplantation. It has been estimated that the incidence of non-viral infectious keratitis is 28 per 100,000 person-years in the USA. Internationally, and particularly in tropical regions, the incidence may be much higher. For example, in one district in India, the incidence was found to be 11 per 10,000 persons-years. The monocular vision loss associated with corneal ulceration has been shown to reduce vision-related quality of life.

The first step to the treatment of bacterial infection is to achieve microbiological cure. Clinicians weigh many factors when choosing an antibiotic regimen: broad-spectrum coverage, toxicity, availability and cost, and region-specific epidemiology of pathogens and resistance patterns. We surveyed the Cornea Society regarding empiric antibiotic choice for presumed bacterial ulcers. Despite its toxicity, 55% (n=57) of US physicians used fortified topical vancomycin as their first choice due to concerns over the emergence of resistant organisms such as methicillin-resistant *Staphylococcus aureus*. However, a recent review of high-quality, randomised controlled clinical trials on the management of bacterial keratitis with topical antibiotics identified no antibiotic strategy that produced a significant difference in the relative risk of treatment success, defined as complete re-epithelialisation of the cornea or on time to cure. Therefore, we may not be able to dramatically improve clinical outcomes by antibiotic choice alone.

Even if infectious organisms are eliminated, poor vision can result from corneal opacity and irregular astigmatism. The use of adjuvant corticosteroids has long been debated in the treatment of bacterial keratitis. Proponents argue that they decrease inflammation and reduce scarring, neovascularisation and stromal melt. However, others argue that corticosteroids delay epithelial healing and prolong infection. Three small randomised controlled trials examining the benefit of adjuvant topical steroids for the treatment of corneal ulcers found no difference in visual acuity outcomes or healing times between those randomised to topical antibiotic alone versus topical antibiotic plus topical steroid.

The Steroids for Corneal Ulcers Trial is by far the largest randomised controlled trial to have evaluated the role of adjunctive steroids for bacterial ulcers. Five hundred study participants with culture-positive bacterial ulcers were enrolled at the University of California, San Francisco, at Aravind Eye Hospitals in Madurai, Coimbatore and Tirunelveli in India, and at the Dartmouth-Hitchcock Medical Center in New Hampshire. Patients were randomised to receive either topical prednisolone sodium phosphate 1.0% or topical placebo (sodium chloride 0.9%), started after 48 hours of topical moxifloxacin 0.5%. All patients received one drop of their assigned treatment four times daily for the first week after enrolment, then two times daily for the second week, and then one time daily for the third week. After controlling for baseline BSCVA a multiple linear regression showed that corticosteroids provided no significant improvement in 3-month BSCVA over placebo (p=0.82). Similarly, there was no difference between arms in secondary outcomes, such as rate of re-epithelialisation (p=0.25), infiltrate/sar scar size (p=0.40) or the number of perforations observed (p=0.99). It is also important to note that corticosteroids did not cause an increase in adverse events.

Post-hoc subgroup analyses have suggested that earlier treatment of large, central, non- *Nocardia* ulcers did have improved visual acuity outcomes compared with antibiotic alone (figure 1). A 12-month SCUT analysis excluding *Nocardia* ulcers found a one-line visual acuity benefit among those randomised to topical steroid. We also found that those treated with steroid earlier, within 2–3 days of antibiotics, had one-line better visual acuity.
at 3 months. These subgroup analyses have led some to conclude that topical corticosteroids may be beneficial for specific subgroups of culture-positive bacterial ulcers and that they were most effective when administered early with appropriate antibiotics.5 6

CXL may benefit patients with infectious corneal ulcers through direct antimicrobial and anti-inflammatory effects, as well as increased resistance of corneal tissue to enzymatic degradation.7 8 9 Photoactivation of riboflavin with UV light results in release of reactive species that promote chemical covalent bond formation between adjacent collagen molecules.10 11 Reactive triplets are also thought to have an antiseptic effect against a broad range of pathogens.12 Cross-linked corneas have also shown increased in vitro resistance to keratolysis by collagenase A.13 CXL is currently used as a treatment for corneal ectatic disorders such as keratoconus and post-Laser-Assisted In Situ Keratomileusis (LASIK) ectasia and has been shown to stiffen the cornea and allow it to retain its normal shape.14 15 16 Immediately after CXL there is a decrease in the subepithelial nerve plexus and loss of keratocytes in the anterior one-third of the corneal stroma, although this recovers after a few months.17 18 CXL would presumably destroy inflammatory cells in the anterior stroma by similar mechanisms, although this does not appear to have been studied previously.

To date, few prospective clinical trials have been conducted to assess the effect of CXL in the treatment of bacterial keratitis. Bamdad et al19 randomised 32 patients with moderate bacterial keratitis to receive either CXL plus standard therapy versus standard therapy alone. Two weeks after the treatment, those receiving CXL had a lower mean grade of ulcer (0.69 vs 1.70; p<0.001), smaller area of epithelial defect (p=0.001) and smaller area of infiltrate (p<0.001) than those receiving standard therapy alone. The mean treatment duration was also shorter in the CXL group (p<0.001). Another trial randomised patients with bacterial, fungal, Acanthamoeba or mixed origin keratitis to CXL versus antimicrobial treatment alone.20 While this trial found no difference between groups, it had multiple issues, including inappropriate randomisation, vastly different aetiologies of infection and insufficient power.21 One non-randomised prospective series of 40 patients found a decreased rate of perforation among those treated with CXL compared with controls despite the fact they had on average larger baseline ulcer size.22 Given the limitations of these studies and mixed results, it is not known whether CXL is a beneficial adjuvant therapy for infectious keratitis, and a well-designed, larger scale randomised clinical trial is warranted. A recent meta-analysis concluded that CXL may be beneficial in patients with infectious keratitis.23

There are several limitations to the design of this study to consider. It will still be important to measure the effect of CXL on clinical outcomes such as visual acuity and scar size. A number of studies have demonstrated the safety and efficacy of CXL for the treatment of keratoconus with follow-up in the range of 5–10 years.24 However, the observed corneal flattening associated with improved visual acuity outcomes in keratoconus could result in unexpected topographic changes in infectious keratitis and it is not known what effect CXL has on corneal scarring in these cases.

Detecting differences in clinical outcomes for corneal ulcer trials has proven difficult. Surrogate outcomes have become popular as they often require smaller sample sizes and result in faster trial completion as they allow detection of response to treatment at an earlier stage. In addition to evaluating clinical outcomes such as best spectacle-corrected visual acuity and scar size, we will be evaluating a number of other potential indicators of response to treatment that may prove to be more sensitive outcomes for future clinical trials. One alternative approach could be to use microbiological cure as the primary outcome. Although the ultimate goals of therapy in bacterial ulcer treatment are corneal ulcer healing, improved visual acuity and vision-related quality of life, culture positivity is highly correlated with clinical outcomes. SCUT found that decreased antibiotic susceptibility resulted in decreased visual acuity outcomes and increased scar size.25

CONCLUSION
The results of this study are expected to provide evidence of the efficacy of CXL and early steroids as adjunctive treatments in bacterial keratitis. We anticipate that these therapies will improve outcomes such as visual acuity, while reducing the rate of complications such as perforation or the need for therapeutic penetrating keratoplasty.

TRIAL STATUS
This protocol is version 2.0, dated 17 July 2020. Recruitment began on 24 September 2020 and is expected to last until approximately September 2023.

Author affiliations
1Aravind Eye Hospital, Madurai, Tamil Nadu, India
2Cornea, Aravind Eye Care System, Madurai, Tamil Nadu, India
3Microbiology, Aravind Eye Hospital, Madurai, India
4Cornea, Aravind Eye Hospital, Pondicherry, India
5Cornea, Aravind Eye Hospital, Coimbatore, Tamil Nadu, India
6Dept of Ophthalmology, University of Miami Health System Bascom Palmer Eye Institute, Miami, Florida, USA
7Fl Proctor Foundation, University of California, San Francisco, San Francisco, California, USA
8Department of Ophthalmology, University of California, San Francisco, San Francisco, California, USA
9Dept of Ophthalmology, University of California, San Francisco, California, USA
10Ophthalmology, University of California, San Francisco, San Francisco, California, USA
11Byers Eye Institute, Dept of Ophthalmology, Stanford University, California, San Francisco, USA

Acknowledgements: Riboflavin for the US enrolled patients was donated by Avedro. They will not have input into the study design, analysis or writing of the manuscript.

Contributors: TML, JR-N, VNP and NR have contributed to the design of the study and study implementation and these collaborators make up the steering committee. TML is the head of the data coordinating centre. JR-N is the head of the coordinating centre. LSP, AV, RR and GA are contributing to study
implementation, TCP is the biostatistician and as such has directed the statistical analysis plan and will have access to the final data set.

**Funding** This work was supported by grants U61 EY028518 (TML/JR-N) and K23 EY25025 (JR-N) from the National Eye Institute and Research to Prevent Blindness (UCSF).

**Competing interests** None declared.

**Patient consent for publication** Consent obtained directly from patient(s).

**Ethics approval** Single IRB approval for US sites was obtained at the University of California, San Francisco. Institutional IRB approval was obtained at the Aravind Eye Hospital, Madurai and Pondicherry. Indian Council of Medical Research (ICMR) approval was also obtained for the study.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**
Venkatnath N Prjna http://orcid.org/0000-0003-2019-4044
Lalitha S Prjna http://orcid.org/0000-0001-5379-7015
Travis C Porho http://orcid.org/0000-0001-8813-3171
Jennifer Rose-Nussbaum http://orcid.org/0000-0002-4905-2528

**REFERENCES**

1. McDonald EM, Ram FSF, Patel DV, et al. Topical antibiotics for the management of bacterial keratitis: an evidence-based review of high quality randomised controlled trials. Br J Ophthalmol 2014;98:1470–7.

2. Tan DTH, Jananathapan P, Zhou H, et al. Penetrating keratoplasty in Asian eyes: the Singapore corneal transplant study. Ophthalmology 2008;115:e971:975–82.

3. Hobden JA, Pseudomonas aeruginosa proteases and corneal virulence. DNA Cell Biol 2002;21:391–6.

4. Matsumoto K. Role of bacterial proteases in pseudomonal and staphylococcal keratitis. Biol Chem 2004;385:1007–16.

5. Ray KJ, Srinivasan M, Mascalresnha J, et al. Early addition of topical corticosteroids in the treatment of bacterial keratitis. JAMA Ophthalmol 2014;132:737–41.

6. Pillaua S, Henry CR, Amescua G, et al. Role of steroids in the treatment of bacterial keratitis. JAMA Ophthalmol 2013;131:1089–94.

7. Alio JL, Pseudomonas aeruginosa proteases and corneal virulence. Br J Ophthalmol 2013;97:512–20.

8. Blaauw J, She R, Shulman IA, et al. Microbial keratitis in Los Angeles: the doheny eye institute and the Los Angeles county hospital experience. Ophthalmology 2015;122:918–24.

9. Papaioannou L, Miglikos M, Papaathanassiou M. Corneal collagen cross-linking for infectious keratitis: a systematic review and meta-analysis. Cornea 2016;35:62–71.

10. Martins SR, Combs JC, Noguera G, et al. Antimicrobial efficacy of riboflavin/UVA combination (365 nm) in vitro for bacterial and fungal isolates: a potential new treatment for infectious keratitis. Invest Ophthalmol Vis Sci 2008;49:3407–14.

11. Panda A, Krishna SN, Kumar S. Photo-activated riboflavin therapy of refractory corneal ulcers. Cornea 2012;31:1210–3.

12. Iseki HP, Thiel MA, Hafezi F, et al. Ultraviolet A/riboflavin corneal cross-linking for infectious keratitis associated with corneal melts. Cornea 2008;27:590–4.

13. Makioumi K, Mortensen J, Saus MK, et al. Collagen crosslinking in the management of advanced non-resolving microbial keratitis. Br J Ophthalmol 2014;98:1033–5.

14. Shetty R, Nagaraja H, Jayadev C, et al. Corneal collagen crosslinking in the management of advanced non-resolving microbial keratitis. Br J Ophthalmol 2014;98:1033–5.

15. McLeod SD, Kolahdouz-Ishahani A, Rostamian K, et al. The role of smears, cultures, and antibiotic sensitivity testing in the management of suspected infectious keratitis. Ophthalmology 1996:103:23–8.

16. Ray KJ, Lalitha P, Prjna NV, et al. The utility of repeat culture in fungal corneal ulcer management: a secondary analysis of the MURT-I randomized clinical trial. Am J Ophthalmol 2017;178:157–62.

17. Bhadange Y, Das S, Kasav MK, et al. Comparison of culture-negative and culture-positive microbial keratitis: cause of culture negativity, clinical features and final outcome. Br J Ophthalmol 2015;99:1498–502.

18. McLeod SD, Kolahdouz-Ishahani A, Rostamian K, et al. The role of smears, cultures, and antibiotic sensitivity testing in the management of suspected infectious keratitis. Ophthalmology 1996:103:23–8.

19. Vemuganti G, Garg P, Gopinathan U, et al. Evaluation of agent and host factors in progression of mycotic keratitis: a histologic and microbiologic study of 167 corneal buttons. Ophthalmology 2002:109:1538–46.

20. Whitcher JP, Srinivasan M, Upadhyay MP, Corneal blindness: a global perspective. Bull World Health Organ 2001;79:214–21.

21. ABKP. Bacterial keratitis preferred practice pattern (ppp) guideline. 2013. In: American Academy of Ophthalmology, 2013.

22. Jang BH, Gritz DC, Kumar AB, et al. Epidemiology of ulcerative keratitis in Northern California. Arch Ophthalmol 2010;128:1022–8.

23. Gonzales CA, Srinivasan M, Whitcher JP, et al. Incidence of corneal ulceration in Madurai district, South India. Ophthalmic Epidemiol 1996:3:159–66.

24. Rose-Nussbaum J, Prjna NV, Krishnan KT, et al. Vision-Related quality-of-life outcomes in the mycotic ulcer treatment I: a randomized clinical trial. JAMA Ophthalmol 2015;133:642–6.

25. Auer A, Schallhorn J, Geske M, et al. Empirical treatment of bacterial keratitis: an international survey of corneal specialists. BMJ Open Ophthalmol 2017;2: doi:10.1136/bmjophth-2016-000047. [Epub ahead of print: 16-08-2017].

26. Acharya NR, Srinivasan M, Mascalresnha J, et al. The steroid controversy in bacterial keratitis. Arch Ophthalmol 2009;127:1231.

27. Cohen EJ, The case against the use of steroids in the treatment of bacterial keratitis. Arch Ophthalmol 2009;127:103–4.

28. Hindman HB, Patel SB, Jun AS. Rationale for adjunctive topical corticosteroids in bacterial keratitis. Arch Ophthalmol 2009;127:97–102.

29. Den S, Sotozono C, Kinoshita S, et al. Efficacy of early systemic betamethasone or cyclosporin A after corneal alkali injury via inflammatory cytokine reduction. Acta Ophthalmol Scand 2004;82:195–9.

30. Yi K, Chung TY, Hoon YJ. Combined treatment with antioxidants and immunosuppressants on cytokine release by human peripheral blood mononuclear cells - chemically injured keratoacyte reaction. Mol Vis 2011;17:2665–71.

31. Williams RN, Paterson CA. The influence of topical corticosteroid therapy upon polymorphonuclear leukocyte distribution, vascular integrity and ascorbate levels in endotoxin-induced inflammation of the rabbit eye. Exp Eye Res 1987;44:191–8.

32. Chung J-H, Kang Y-G, Kim H-J. Effect of 0.1% dexamethasone on epithelial healing in experimental corneal alkali wounds: morphological changes during the repair process. Graefes Arch Exp Clin Ophthalmol 1998;236:537–45.

33. Tomas-Barberan S, Fagerholm P. Influence of topical treatment on epithelial wound healing and pain in the early postoperative period following photorefractive keratectomy. Acta Ophthalmol Scand 1999;77:135–8.

34. Gritz DC, Kwitko S, Trousdale MD, et al. Recurrence of microbial keratitis concomitant with antiinflammatory treatment in an animal model. Cornea 1992;1:114–8.

35. Gritz DC, Lee TY, Kwitko S, et al. Topical anti-inflammatory agents in an animal model of microbial keratitis. Arch Ophthalmol 1990;108:1001–5.

36. Blair J, Hodge W, Al-Ghamdi S, et al. Comparison of antibiotic-only and antibiotic-steroid combination treatment in corneal ulcer patients: double-blinded randomized clinical trial. Can J Ophthalmol 2011;46:40–5.

37. Carmichael TR, Geifand Y, Welsh NH. Topical steroids in the treatment of central and paracentral corneal ulcers. Br J Ophthalmol 1990;74:528–31.

38. Srinivasan M, Lalitha P, Mahalakshmi R, et al. Corticosteroids for bacterial corneal ulcers. Br J Ophthalmol 2009;93:198–202.
39 Srinivasan M, Mascarenhas J, Rajaraman R, et al. Corticosteroids for bacterial keratitis: the steroids for corneal ulcers trial (SCUT). *Arch Ophthalmol* 2012;130:143–50.

40 Srinivasan M, Mascarenhas J, Rajaraman R, et al. The steroids for corneal ulcers trial (SCUT): secondary 12-month clinical outcomes of a randomized controlled trial. *Am J Ophthalmol* 2014;157:e323:327–33.

41 Cherfan D, Verter EE, Melki S, et al. Collagen cross-linking using rose Bengal and green light to increase corneal stiffness. *Invest Ophthalmol Vis Sci* 2013;54:3426–33.

42 Kamaev P, Friedman MD, Sherr E, et al. Photochemical kinetics of corneal cross-linking with riboflavin. *Invest Ophthalmol Vis Sci* 2012;53:2380–7.

43 Vatansever F, de Melo WCMA, Avci P, et al. Antimicrobial strategies centered around reactive oxygen species–bactericidal antibiotics, photodynamic therapy, and beyond. *FEMS Microbiol Rev* 2013;37:955–89.

44 Arafat SN, Robert M-C, Shukla AN, et al. UV cross-linking of donor corneas confers resistance to keratolysis. *Cornea* 2014;33:955–9.

45 Keating A, Pineda R, 2Nd, Colby K. Corneal cross linking for keratoconus. *Semin Ophthalmol* 2010;25:249–55.

46 Lamy R, Netto CF, Reis RG, et al. Effects of corneal cross-linking on contrast sensitivity, visual acuity, and corneal topography in patients with keratoconus. *Cornea* 2013;32:591–6.

47 Raiskup-Wolf F, Hoyer A, Spoerl E, et al. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg* 2008;34:796–801.

48 Vinciguerra P, Albè E, Trazza S, et al. Intraoperative and postoperative effects of corneal collagen cross-linking on progressive keratoconus. *Arch Ophthalmol* 2009;127:1258–65.

49 Mazzotta C, Hafezi F, Kymionis G, et al. In vivo confocal microscopy after corneal collagen crosslinking. *Ocul Surf* 2015;13:298–314.

50 Sharma N, Suri K, Sehra SV, et al. Collagen cross-linking in keratoconus in Asian eyes: visual, refractive and confocal microscopy outcomes in a prospective randomized controlled trial. *Int Ophthalmol* 2015;35:827–32.

51 Bamdad S, Malehosseini H, Khosravi A. Ultraviolet A/riboflavin collagen cross-linking for treatment of moderate bacterial corneal ulcers. *Cornea* 2015;34:402–6.

52 Said DG, Elafy MS, Gatziofus Z, et al. Collagen cross-linking with photoactivated riboflavin (PACK-CXL) for the treatment of advanced infectious keratitis with corneal melting. *Ophthalmology* 2014;121:1377–82.

53 Mittal R, Garg P, Re: Said et al.: Collagen cross-linking with photoactivated riboflavin (PACK-CXL) for the treatment of advanced infectious keratitis with corneal melting. *Ophthalmology* 2014;121:1377–82. *Ophthalmology* 2014;121:e67–8.

54 Marasini S, Zhang AC, Dean SJ, et al. Safety and efficacy of UV application for superficial infections in humans: a systematic review and meta-analysis. *Ocul Surf* 2021;21:331–44.

55 El Rami H, Chelala E, Dirani A, et al. An update on the safety and efficacy of corneal collagen cross-linking in pediatric keratoconus. *Biomed Res Int* 2015;2015:1–7.

56 Lalitha P, Srinivasan M, Manikandan P, et al. Relationship of in vitro susceptibility to moxifloxacin and in vivo clinical outcome in bacterial keratitis. *Clin Infect Dis* 2012;54:1381–7.