Cross-Linking Assisted Infection Reduction (CLAIR): A Randomized Clinical Trial Evaluating the Effect of Adjuvant Cross-Linking on Bacterial Keratitis

N. Venkatesh Prajna, Naveen Radhakrishnan,* Prajna Lalitha,* Revathi Rajaraman,* Shivananda Narayana, MS,* Ariana F. Austin,† Zijun Liu,† Jeremy D. Keenan,†‡ Travis C. Porco,†§ Thomas M. Lietman,†§‡ and Jennifer Rose-Nussbaumer, MD†‡¶*

Purpose: To determine whether there is a benefit to adjuvant corneal cross-linking (CXL) for bacterial keratitis.

Methods: This is an outcome-masked, randomized controlled clinical trial. Consecutive patients presenting with a smear-positive bacterial ulcer at Aravind Eye Hospitals at Madurai, Pondicherry, and Coimbatore in India were enrolled. Study eyes were randomized to topical moxifloxacin 0.5% or topical moxifloxacin 0.5% plus CXL. The primary outcome of the trial was microbiological cure at 24 hours on repeat culture. Secondary outcomes included best spectacle corrected visual acuity at 3 weeks and 3 months, percentage of study participants with epithelial healing at 3 weeks and 3 months, infiltrate and/or scar size at 3 weeks and 3 months, 3-day smear and culture, and adverse events.

Results: Those randomized to CXL had 0.60 decreased odds of culture positivity at 24 hours (95% confidence interval [CI]: 0.10–3.50; $P = 0.65$), 0.9 logarithm of the minimum angle of resolution lines worse visual acuity (95% CI: −2.8 to 4.6; $P = 0.63$), and 0.41-mm larger scar size (95% CI: −0.48 to 1.30; $P = 0.38$) at 3 months. We note fewer corneal perforations or need for therapeutic penetrating keratoplasty in the CXL group.

Conclusions: We were unable to confirm a benefit to adjuvant CXL in the primary treatment of moderate bacterial keratitis. However, CXL may reduce culture positivity and complication rates; therefore, a larger trial to fully evaluate this is warranted.

Received for publication May 20, 2020; revision received July 18, 2020; accepted July 20, 2020. Published online ahead of print October 16, 2020.

From the *Aravind Eye Hospitals, Madurai, Coimbatore, Pondicherry, India; †Francis I. Proctor Foundation, University of California San Francisco, CA; ‡UCSF Department of Ophthalmology, University of California, San Francisco, CA; §UCSF Epidemiology and Biostatistics, University of California, San Francisco, CA; and ¶Kaiser Permanente Northern California, Redwood City, CA.

The authors have no funding or conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.corneajrnl.com).

Correspondence: Jennifer Rose-Nussbaumer, MD, Kaiser Permanente Northern California, UCSF/Proctor Foundation, 513 Parnassus Avenue, S347 San Francisco, CA 94143 (e-mail: jennifer.rose-nussbaumer@ucsf.edu).

Trial Registration: NCT02570321.

Key Words: infectious keratitis, corneal cross-linking, bacterial ulcer

(*Cornea* 2021;40:837–841)

Although antibiotics are successful at achieving microbiological cures in infectious keratitis, outcomes are often poor if the ulcer is large, central, or resistant to antibiotics. Corneal cross-linking (CXL) is a novel proposed therapy that may directly reduce bacterial pathogens and increase the resistance of corneal tissue to enzymatic degradation.[1,2] Photochemically activated riboflavin inhibits the growth of common bacteria such as *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* in vitro.[2] Multiple case reports have suggested symptomatic improvement, treatment of drug-resistant organisms, and treatment of corneal melt as other potential benefits of CXL.[3–6] In 1 series of patients, bacterial keratitis resolved although patients were treated exclusively with CXL.[7] Here, we evaluate adjuvant CXL as a primary treatment of moderate-to-severe bacterial keratitis.

METHODS

Cross-Linking Assisted Infection Reduction was an outcome-masked, clinical trial, randomizing patients presenting with a smear-positive bacterial ulcer to topical moxifloxacin 0.5% alone versus moxifloxacin 0.5% plus CXL. Ethical approval was obtained from the University of California, San Francisco, Committee on Human Research (IRB #14-14918) and the Aravind Eye Care System Institutional Review Board, Madurai and Pondicherry, India. Written informed consent was obtained from all participants, and the trial conformed to the tenets of the Declaration of Helsinki.[8]

Outcomes

The prespecified primary outcome of the trial was microbiological cure at 24 hours on repeat culture. Secondary outcomes included the 24-hour smear result, best spectacle corrected visual acuity (BSCVA) at 3 weeks and 3 months, percentage of epithelial healing at 3 weeks and 3 months, infiltrate and/or scar size at 3 weeks and 3 months, and

adverse events including corneal perforation or the need for therapeutic penetrating keratoplasty (TPK).

Study Participants

All study participants were enrolled at Aravind Eye Hospitals in Madurai, Coimbatore, and Pondicherry, India. Consecutive patients who presented with corneal ulcers were screened for inclusion. Inclusion criteria were a visual acuity of 20/70 (logarithm of the minimum angle of resolution [LogMAR] 0.54) or worse in the affected eye and the presence of corneal ulcer that was smear positive for bacteria. Exclusion criteria included central pachymetry less than 350 μm, evidence of concomitant infection with fungus or herpes, impending or frank perforation or limbal involvement, no light perception vision in the affected eye or visual acuity worse than 20/200 in the unaffected eye, age younger than 18 years or greater than 70 years, and patients who were unable to complete the follow-up. Once randomized, participants were included in the intent-to-treat analysis.

Interventions

Microbiological methods used for this study were adapted from a protocol used in the Mycotic Ulcer Treatment Trial that has been previously published.[9] Corneal scraping was performed at enrollment and at 24 hours and 3 days after enrollment by a masked microbiologist. A Kimura spatula using aseptic techniques was used to obtain a scrape from the leading edge and base of the corneal ulcer. Two scrapings were smeared directly onto 2 separate glass microbiology slides for Gram stain and for potassium hydroxide (KOH) wet mount, whereas 3 additional scrapings were taken and directly inoculated onto sheep blood agar, chocolate agar, potato dextrose agar, or Sabouraud agar for bacterial and fungal cultures. A positive bacterial smear was defined as bacteria seen under low-power magnification and reduced light. Positive bacterial cultures were defined as light growth on any 2 media or moderate-to-heavy growth on 1 medium.

All patients received topical moxifloxacin 0.5% (Aurolab, Madurai, India) every hour and were hospitalized for the first 3 days; all medications were directly observed and recorded by a health technician. For those randomized to CXL, the procedure was performed within 24 hours of enrollment and followed a modified Dresden protocol, whereby only the epithelium around the infiltrate was scrapped. Using sterile techniques, a 30-minute loading dose of topical drops comprising 0.1% riboflavin with 20% dextran 500 (Intacs XL, India) was administered every 2 minutes. The cornea was then exposed to UV-A light at a wavelength of 365 nm with an irradiance of 3 mW/cm^2 for 30 minutes and topical riboflavin at 5-minute intervals (Intacs XL).

Participants were examined at each study visit with a slit-lamp biomicroscope by a certified masked ophthalmologist to assess the epithelial defect size, infiltrate, and/or scar dimensions and depth according to a protocol adapted from the Herpetic Eye Disease Study.[10] Age-Related Eye Disease Study using Early Treatment Diabetic Retinopathy Study BSCVA was recorded at 4 m by a certified masked refractionist.[11] Low vision testing was also performed at a distance of 0.5 m.

Masking

The microbiologist, treating physician involved in the outcome assessment, and refractionist performing BSCVA were all masked to the treatment arm. The surgeon performing CXL and study participants were not masked to CXL intervention status but were asked not to share this information with any of the study personnel.

Sample Size Calculation

We estimate that a sample size of 36 eyes would provide at least 80% power to detect a 0.48 LogMAR difference (~5 Snellen lines), assuming a 2-tailed alpha of 0.05 and a SD of visual acuity at 3 months of 0.63 LogMAR.

TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristic	Moxifloxacin Only (N = 19)	Moxifloxacin + CXL (N = 17)
Sex, no. (%)		
Male	13 (68)	8 (47)
Female	6 (32)	9 (53)
Age, median (IQR), y	60 (54.5–65)	59 (48–66)
Occupation, no. (%)		
Agriculture	12 (63)	8 (47)
Nonagriculture	6 (32)	9 (53)
Contact lens related, no. (%)	0 (0)	0 (0)
Medication use at enrollment, no. (%)*	8 (42)	10 (59)
Trauma, no. (%)*,†	11 (58)	9 (53)
Affected eye, no. (%)		
Right	11 (58)	9 (53)
Left	8 (42)	8 (47)
Visual acuity, median (IQR)		
LogMAR	1.7 (0.7–1.7)	1.7 (0.6–1.8)
Approx. Snellen	CF (20/100, CF)	CF (20/80, HM)
Ulcer location, no. (%)		
Central	14 (74)	13 (76)
Peripheral	4 (21)	4 (24)
Infiltrate and/or scar, median (IQR), mm‡	3.5 (2.7–4)	3 (2.24–4)
Hypopyon, no. (%)		
No	6 (32)	6 (35)
<0.5 mm	2 (11)	1 (6)
≥0.5 mm	11 (58)	10 (59)
% depth, no. (%)*		
>0%–33%	5 (26)	6 (35)
>33%–67%	10 (53)	10 (59)
>67%–100%	4 (21)	1 (6)
Epithelial defect, median (IQR), mm‡	3.2 (2.3–3.9)	3 (2.2–3.5)
Duration of symptoms, median (IQR), d	3 (2–5)	4 (3–14)

*Missing data.
†Includes fall, mattress, metal wire, mud, nail, sand, and wood.
‡Geometric mean.
CF, count fingers; HM, hand motion; IQR, interquartile range; LP, light perception; No., number.

Statistical Analysis

The prespecified primary analysis used a logistic regression model to assess microbiological cure at 24 hours between the groups controlling for baseline culture status. Similar logistic regression models were used to assess the percentage with healed epithelium and controlling for baseline culture status or the geometric mean size of the baseline epithelial defect. Multiple linear regression was used to analyze BSCVA and infiltrate and/or scar size with baseline measurements as covariates. Because of the small sample size, statistical significance was assessed using Monte Carlo permutation.[12] Adverse events were reported and tabulated by arms. For missing data, we used the last observation carried forward. All analyses were conducted using R performed during the week of October 11, 2019.

RESULTS

A total of 36 patients with smear-positive ulcer were randomized (see Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B99). Follow-up was available for 35 patients (97%) for the primary analysis and 33 patients (92%) at 3 months. Participants were well matched between groups for demographic and clinical characteristics, although there were slightly more women randomized to CXL (Table 1). Approximately half of the study participants worked in agriculture, with trauma being the most common etiology of infection. None of the ulcers were related to contact lens use. Table 2 outlines the organisms isolated in the culture; *S. pneumoniae* (N = 13, 36%) and *Pseudomonas* species (N = 6, 17%) were the most common.

Table 3 outlines the primary and secondary outcomes. Ulcers treated with CXL showed an odds ratio of 0.60 for culture positivity at 24 hours (95% confidence interval [CI]: 0.10–3.50; $P = 0.65$). Those randomized to CXL had 1.6 LogMAR worse visual acuity at 3 weeks (95% CI: −1.4 to 4.7; $P = 0.29$) and 0.9 LogMAR worse visual acuity at 3 months (95% CI: −2.8 to 4.6; $P = 0.62$) after controlling for baseline visual acuity. CXL patients had 0.60-mm larger scar size at 3 weeks (95% CI: −0.16 to 1.35; $P = 0.11$) and 0.41-mm larger scar size at 3 months (95% CI: −0.48 to 1.30; $P = 0.38$). At 3 weeks, those randomized to CXL had an odds ratio of 0.99 of being epithelialized (95% CI: 0.70–1.44; $P = 0.99$). We note fewer corneal perforations and TPKs in the CXL group (N = 1, 6%) versus medication along (N = 4, 21%).

DISCUSSION

In this therapeutic exploratory trial, we were unable to show a benefit to adjuvant CXL in the primary treatment of bacterial ulcers. However, it is interesting that those randomized to CXL in our study had lower odds of culture positivity at 24 hours compared with controls. 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.[13–16] *In vitro* studies demonstrate that photochemically activated riboflavin generates reactive oxygen species that have an antiseptic effect against common bacterial pathogens, including drug-resistant organisms—such as *Pseudomonas* and MRSA.[17,18]

TABLE 2. Baseline Microbiological Culture Results

Organism	Moxifloxacin Only* (N = 19)	Moxifloxacin + CXL (N = 17)	Total* (N = 36)	Moxifloxacin Susceptibility
S. pneumoniae	10 (53)	3 (18)	13 (36)	S
Nocardia spp	—	2 (12)	2 (6)	S, I†
Staphylococcus coag-negative	—	—	—	S
Staphylococcus aureus	—	—	—	S
Streptococcus viridians group	—	1 (6)	1 (3)	S
Corynebacterium spp	—	—	—	S
Bacillus spp	—	—	—	S
Mycobacterium spp	—	—	—	S
Other Gram positive	—	—	—	S
Pseudomonas aeruginosa	2 (11)	3 (18)	5 (14)	S
Pseudomonas spp (non-aerug)	0 (0)	1 (6)	1 (3)	S
Moraxella spp	1 (5)	2 (12)	3 (8)	S
Klebsiella spp	—	—	—	S
Enterobacter spp	—	—	—	S
Haemophilus	—	—	—	S
Influenzae	—	—	—	S
Other Gram negative	—	—	—	S
Bacterial culture negative	5 (26)	5 (29)	10 (28)	—

*Missing data for 1 patient.

†One patient with intermediate moxifloxacin resistance was switched to fortified 2% amikacin and 5% ampicillin, the patient with susceptibility continued treatment with moxifloxacin but 2% amikacin was added.

A., aspergillus; I, intermediate; No., number; S, sensitive; spp, species.

TABLE 3. Primary and Secondary Outcomes

Outcome	Moxifloxacin Only (N = 19)	Moxifloxacin + CXL (N = 17)	Estimate (95% CI)	P*
Culture positivity, N (%)				
Baseline	13 (68)	12 (71)		
Repeat	11 (58)	8 (47)	OR: 0.60 (0.10 to 3.50)	0.65
Visual acuity, median (IQR)†,‡				
Baseline	1.70 (0.70–1.70)	1.70 (0.60–1.80)		
3 wk§	0.95 (0.65–1.54)	1.10 (0.82–1.80)	1.6 (−1.4 to 4.7)†	0.29
3 mo§	0.82 (0.62–1.40)	1.32 (0.43–1.75)	0.9 (−2.8 to 4.6)†	0.62
Infiltrate/scar, median, mm (IQR)‡				
Baseline	3.50 (2.70–4.00)	3.00 (2.24–4.00)		
3 wk	3.00 (2.91–3.73)	2.50 (2.00–3.46)	0.60 (−0.16 to 1.35)	0.11
3 mo	3.58 (3.00–4.47)	3.74 (2.91–5.24)	0.41 (−0.48 to 1.30)	0.38
Reepithelialized, N (%)				
3 wk§	8 (43)	9 (53)	OR: 0.99 (0.70 to 1.44)	0.99
3 mo§,‖	17 (89)	15 (88)	—	—
Corneal perforation, N (%)	1 (5)	0 (0)	1 (3)	
TPK, N (%)	3 (16)	1 (6)	4 (11)	
Total Perf/TPK, N (%)	4 (21)	1 (6)	5 (14)	

*Each *P*-value given represents a logistic regression model comparing CXL versus no CXL for the stated outcome, controlling for the baseline value. Permutation *P*-values are reported.

†Snellen line = 0.1 LogMAR.

‡Linear regression comparing CXL versus no CXL for the stated outcome, controlling for the baseline value.

§Missing data.

‖All patients reepithelialized.

IQR, interquartile range.

CXL of collagen fibrils should also theoretically strengthen the cornea against enzymatic degradation. Our study demonstrated a lower rate of perforation and TPK in the CXL group, but the overall numbers of these complications were low, likely making it difficult to detect a statistically significant difference. Corneal melting occurs in response to proteolytic enzymes released from both pathogens and leukocytes sent to combat infection.[19,20] Corneal perforation is a devastating complication, often treated with surgical interventions—such as TPK—which have a poor prognosis compared with penetrating keratoplasty (PKP) performed for visual rehabilitation.[21] A recent meta-analysis concluded that the probability that CXL was beneficial in inhibiting melting in patients with infectious keratitis was 85% (95% CI 0.77–0.91).[22]

Two other small prospective clinical trials have been conducted to assess the effect of CXL in the treatment of bacterial keratitis. Bamdad et al[23] randomized 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 randomized patients with bacterial, fungal, *Acanthamoeba*, or mixed origin keratitis to CXL versus antimicrobial treatment alone.[24] Although this trial found no difference between the groups, it had multiple issues, including inappropriate randomization, vastly different etiologies of infection, and insufficient power.[25] According to 1 survey, 96% of CXL experts believed it to be beneficial in the treatment of bacterial keratitis.[26] Given the limitations of these clinical trials and mixed results, it is not known whether CXL is a beneficial adjuvant therapy for infectious keratitis and a well-designed, larger scale randomized clinical trial is warranted.

Limitations to our study include the fact that as a therapeutic exploratory trial, our sample size was small, and there were various ulcer severities enrolled that may have decreased our power to find a difference between the groups. However, all our patients had bacterial ulcers, our ulcer characteristics were well balanced between groups, and we explored early intervention with cross-linking, which is novel. There are important arguments in favor of small studies when exploring new developments, such as cost and feasibility and more value per dollar spent compared with larger studies.[27] In addition, all patients enrolled in this study were from India, and most infections were related to agricultural exposure and not contact lens wear, such as those seen in developed countries. Therefore, it is possible that organisms in this study exhibit different characteristics and response patterns to treatments. This study only evaluated CXL with the modified Dresden protocol; therefore, it is possible that alternative CXL duration or timing (ie, not in the first 24 hours) may produce different results. Finally, new data suggest that CXL with other photosensitizers, such as rose Bengal, may be more effective.[24,28,29]

CONCLUSIONS

Although we were unable to confirm a benefit of CXL as an adjuvant therapy in the treatment of bacterial keratitis in this therapeutic exploratory trial, a larger well-designed

clinical trial is warranted to evaluate the possibility that CXL reduces complications such as corneal melt, perforation, or the need for TPK.

REFERENCES

1. Papaioannou L, Miligkos M, Papathanassiou M. Corneal collagen cross-linking for infectious keratitis: a systematic review and meta-analysis. *Cornea.* 2016;35:62–71.
2. Martins SA, 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;49:3402–3408.
3. Panda A, Krishna SN, Kumar S. Photo-activated riboflavin therapy of refractory corneal ulcers. *Cornea.* 2012;31:1210–1213.
4. Iseli HP, Thiel MA, Hafezi F, et al. Ultraviolet A/riboflavin corneal cross-linking for infectious keratitis associated with corneal melts. *Cornea.* 2008;27:590–594.
5. Makdoumi K, Mortensen J, Crafoord S. Infectious keratitis treated with corneal crosslinking. *Cornea.* 2010;29:1353–1358.
6. Shetty R, Nagaraja H, Jayadev C, et al. Collagen crosslinking in the management of advanced non-resolving microbial keratitis. *Br J Ophthalmol.* 2014;98:1033–1035.
7. Makdoumi K, Mortensen J, Sorkhabi O, et al. UVA-riboflavin photochemical therapy of bacterial keratitis: a pilot study. *Graefes Archive Clin Exp Ophthalmol.* 2012;250:95–102.
8. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310:2191–2194.
9. Prajna NV, Krishnan T, Mascarenhas J, et al. The mycotic ulcer treatment trial: a randomized trial comparing natamycin vs voriconazole. *JAMA Ophthalmol.* 2013;131:422–429.
10. Wilhelmus KR, Gee L, Hauck WW, et al. Herpetic Eye Disease Study. A controlled trial of topical corticosteroids for herpes simplex stromal keratitis. *Ophthalmology*. 1994;101:1883–1895; discussion 1895–1886.
11. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. *Controlled Clin Trials.* 1999;20:573–600.
12. Good PI. *Permutation, Parametric, and Bootstrap Tests of Hypotheses*. New York, NY: Springer Verlag; 2004.
13. Ray KJ, Lalitha P, Prajna NV, et al. The utility of repeat culture in fungal corneal ulcer management: a secondary analysis of the MUTT I randomized clinical trial. *Am J Ophthalmol.* 2017;178:157–162.
14. 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;99:1498–1502.
15. McLeod SD, Kolahdouz-Isfahani A, Rostamian K, et al. The role of smears, cultures, and antibiotic sensitivity testing in the management of suspected infectious keratitis. *Ophthalmology.* 1996;103:23–28.
16. Vemuganti GK, 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;109:1538–1546.
17. Halili F, Arboleda A, Durkee H, et al. Rose bengal- and riboflavin-mediated photodynamic therapy to inhibit methicillin-resistant Staphylococcus aureus keratitis isolates. *Am J Ophthalmol.* 2016;166:194–202.
18. Durkee H, Arboleda A, Aguilar MC, et al. Rose bengal photodynamic antimicrobial therapy to inhibit pseudomonas aeruginosa keratitis isolates. *Lasers Med Sci.* 2020;35:861–866.
19. Hobden JA. Pseudomonas aeruginosa proteases and corneal virulence. *DNA Cell Biol.* 2002;21:391–396.
20. Matsumoto K. Role of bacterial proteases in pseudomonal and serratial keratitis. *Biol Chem.* 2004;385:1007–1016.
21. Tan DT, Janardhanan P, Zhou H, et al. Penetrating keratoplasty in Asian eyes: the Singapore corneal transplant study. *Ophthalmology.* 2008;115:975–982.e971.
22. Alio JL, Abbouda A, Valle DD, et al. Corneal cross linking and infectious keratitis: a systematic review with a meta-analysis of reported cases. *J Ophthalmic Inflamm Infect.* 2013;3:47.
23. Bamdad S, Malekhosseini H, Khosravi A. Ultraviolet A/riboflavin collagen cross-linking for treatment of moderate bacterial corneal ulcers. *Cornea.* 2015;34:402–406.
24. Said DG, Elalfy MS, Gatzioufas Z, et al. Collagen cross-linking with photoactivated riboflavin (PACK-CXL) for the treatment of advanced infectious keratitis with corneal melting. *Ophthalmology.* 2014;121:1377–1382.
25. 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–e68.
26. Hsia YC, Moe CA, Lietman TM, et al. Expert practice patterns and opinions on corneal cross-linking for infectious keratitis. *BMJ Open Ophthalmol.* 2018;3:e000112.
27. Bacchetti P, Deeks SG, McCune JM. Breaking free of sample size dogma to perform innovative translational research. *Sci Transl Med.* 2011;3:87ps24.
28. Ozbek-Uzman S, Yalniz-Akkaya Z, Burcu A. Corneal collagen cross-linking with photoactivated chromophore for infectious keratitis after penetrating keratoplasty. *Cornea.* 2020;39:283–289.
29. Kasetsuwan N, Reinprayoon U, Satitpitakul V. Photoactivated chromophore for moderate to severe infectious keratitis as an adjunct therapy: a randomized controlled trial. *Am J Ophthalmol.* 2016;165:94–99.