Photoactivated Chromophore for Moderate to Severe Infectious Keratitis as an Adjunct Therapy: A Randomized Controlled Trial

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• PURPOSE: **To evaluate the efficacy of photoactivated chromophore for infectious keratitis (PACK-CXL) in the treatment of patients with moderate to severe infectious keratitis as adjunct therapy to the topical medication treatment.**

• DESIGN: **Randomized clinical trial.**

• METHODS: **Thirty eyes from 30 patients with moderate to severe infectious keratitis were randomized to receive either standard treatment plus PACK-CXL (n = 15) or standard treatment alone (control group, n = 15). The primary outcome was the sizes of stromal infiltrates measured on slit-lamp photographs 30 days after treatment. The secondary outcomes were the sizes of epithelial defects, the complication rates, and best pinhole-corrected visual acuity (BPVA).**

• RESULTS: **The median (interquartile range [IQR]) sizes of stromal infiltrates at day 30 were 5.0 mm^2 (0–23.0 mm^2) in the PACK-CXL group and 10.6 mm^2 (1.1–16.3 mm^2) in the control group (median difference 0, 95% CI −7.0 to 0, $P = .66$). The median (IQR) sizes of epithelial defects were 0.7 mm^2 (0–6.3 mm^2) and 4.6 mm^2 (0–10.2 mm^2) in the PACK-CXL group and control group, respectively (median difference −3.0, 95% CI −0.8 to 0, $P = .41$). The complication rates and BPVA after treatment were comparable between groups.**

• CONCLUSIONS: **Standard treatment combined with PACK-CXL did not provide any advantageous effect over standard treatment alone in moderate to severe infectious keratitis over a 30-day period. (Am J Ophthalmol 2016;165:94–99. © 2016 Elsevier Inc. All rights reserved.)**

INFECTIOUS KERATITIS IS A LEADING CAUSE OF RAPID and devastating visual loss worldwide, especially in developing countries. Despite topical broad-spectrum medical therapies being used initially, infectious keratitis leading to corneal perforation or endophthalmitis is not uncommon. A new paradigm-changing treatment able to enhance microbial eradication and improve treatment outcomes with fewer side effects needs to be established.

Corneal collagen cross-linking is a procedure in which the photosensitizer riboflavin and ultraviolet A (UVA) irradiation are used. This procedure preliminarily aims to strengthen the corneal stroma, thereby improving the corneal biomechanics in ectatic corneal disorders.[1] Soon after the acceptance of this concept, corneal cross-linking was proposed to be effective for treating infectious keratitis based on the disinfectant properties of photoactivated chromophore. The possible mechanisms include inhibition of microbial replication, intercalation of the chromophore with microbial nucleic acid,[2] direct damage to the pathogen cell walls by reactive oxygen free radicals,[3,4] increased resistance of the cross-linked cornea to enzymatic damage, and changing of the ocular surface environment.[5] However, the clinical evidence in terms of collagen cross-linking efficacy for keratitis is still inconclusive.[6–9]

In this study, we evaluated the efficacy of photoactivated chromophore for infectious keratitis (PACK-CXL) as an adjunct to medical treatment for patients with moderate to severe infectious keratitis.

METHODS

THE INSTITUTIONAL REVIEW BOARD, FACULTY OF MEDICINE, Chulalongkorn University approved and monitored this randomized controlled trial, which adhered to the tenets of the Declaration of Helsinki. The trial was registered with clinicaltrials.gov (NCT01831206). The sample size for the study was calculated using a superiority design formula with power of 0.8 and a 2-tailed significance level of .05 to detect 7 mm^2 difference in areas of stromal infiltration with standard deviation of 6. This provided a sample size of 15 patients per group. Written informed consent was obtained from all participants.

The participants were recruited from the Department of Ophthalmology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand from March 2013 to December 2014. All patients presenting with infectious keratitis underwent ophthalmic examination including best pinhole-corrected visual acuity (BPVA), slit-lamp biomicroscopy, anterior

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TABLE 1. Baseline Characteristics of Participants With Moderate to Severe Infectious Keratitis in the Medical Therapy Plus Photoactivated Chromophore Group and Medical Therapy Group

Parameter	PACK-CXL Group (n = 15)	Control Group (n = 15)
Mean age (range), y	44.60 (17–73)	53.93 (15–84)
Male-to-female ratio	11:4	10:5
Moderate to severe infectious keratitis ratio	2:13	4:11
Median size of epithelial defect (IQR), mm^2	31.29 (13.48–41.61)	31.11 (19.13–45.94)
Median size of stromal infiltration (IQR), mm^2	31.89 (28.52–62.78)	31.07 (17.93–54.88)
Hypopyon	9/15 (60%)	7/15 (46.67%)
Mean initial BPVA (logMAR)	1.75 ± 0.22	1.68 ± 0.32
Etiologic organisms		
- Bacteria	7/15 (46.67%) - 1 *Pseudomonas* spp - 1 *Enterobacter* spp - 5 negative laboratory results	5/15 (33.33%) - 4 *Pseudomonas* spp - 1 negative laboratory result
- Fungus	8/15 (53.33%) - 2 *Fusarium* spp - 1 *Aspergillus* spp - 1 *Purpureocillium* spp - 1 *Pythium* spp - 2 negative laboratory results	10/15 (66.77%) - 5 unidentified septate hyphae - 1 unidentified budding yeast - 1 *Pythium* spp - 3 negative laboratory results

BPVA = best pinhole-corrected visual acuity; IQR = interquartile range.
PACK-CXL group = medical therapy plus photoactivated chromophore; Control group = medical therapy alone.

segment photography, and posterior segment ultrasonography. The severity of keratitis was graded by slit-lamp biomicroscopy using a modification of Jones's grading.[10] Ulcers that were 2-6 mm in size and infiltration that involved the mid stroma but not beyond the posterior one third of the corneal stroma were graded as moderate infectious keratitis. Ulcers either involving the posterior one third of the cornea or that were more than 6 mm in size were graded as severe infectious keratitis.

Consecutive cases of patients aged older than 6 years with moderate to severe infectious keratitis were enrolled in the study. Pregnant patients or patients with a history or evidence of herpetic keratitis, parasitic keratitis, corneal perforation, autoimmune diseases, endophthalmitis, or corneal thickness less than 400 μm by ultrasound pachymetry were excluded.

After enrollment, participants were randomized to receive standard treatment with or without PACK-CXL using simple randomization. Sealed envelopes, used to conceal the randomization, were opened after enrollment of each participant. A microbiological evaluation included Gram stain, KOH preparation, and cultures; the samples were obtained by corneal scraping in all participants.

Participants randomized to standard treatment received standard medical therapy according to the patient's history, clinical findings, and initial laboratory results. The primary medical therapy for bacterial keratitis included hourly instillation of fortified cefazolin (50 mg/mL; BIOLAB, Samutprakarn, Thailand) and fortified amikacin (20 mg/mL; Atlantic Lab, Bangkok, Thailand); the primary medical therapy for fungal keratitis included hourly topical application of amphotericin B (1.0 mg/mL; Bharat Serums and Vaccines, Maharashtra, India) and topical natamycin (50 mg/mL; Alcon, Bangkok, Thailand). In case of positive clinical response, the medications were tapered based on the judgment of 1 clinician (N.K.). However, if the ulcers progressed, the regimens were changed according to the results of the microbiological evaluation. All participants were treated as inpatients until the medications were tapered to applications of fewer than 4 times a day. No topical or systemic corticosteroids were used during the study period.

For the participants randomized to PACK-CXL, corneal collagen cross-linking with UVA and riboflavin was performed under topical anesthesia on the first day of presentation. The corneal limbus was shielded by a Merocel ring (Medtronic, Inc, Dublin, Ireland). Riboflavin (Medio-CROSS [Peschke Meditrade GmbH, Germany] 0.1% riboflavin/20% dextran solution) was administered to the cornea every 2 minutes for an initial period of 30 minutes and then every 5 minutes for a further 30 minutes during UVA illumination. The epithelium was not removed as there were epithelial defects overlying the ulcers. The