

CASE REPORT

PHOTO ACTIVATED CHROMOPHORE FOR KERATITIS-CORNEAL CROSS-LINKING AS ADJUVANT TREATMENT FOR BACTERIAL AND FUNGAL CORNEAL ULCER

Pradistya Syifa Yudiasari¹, Angga Fajriansyah², Arief Akhdestira Mustaram², Patriotika Muslima², Elfa Ali Idrus²

¹Department of Ophthalmology, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia

²Department of Ophthalmology, Faculty of Medicine, Padjadjaran University, Cicendo National Eye Hospital, Bandung, Indonesia

ABSTRACT

Introduction: Corneal ulcer is a leading cause of blindness worldwide. Many of these patients did not respond to conventional treatment with topical agents. Photo Activated Chromophore for Keratitis - Corneal Cross-Linking (PACK-CXL) has been suggested to treat bacterial and fungal corneal ulcer that did not respond to antimicrobial agents.

Purpose : To report a case series of corneal ulcer treated with PACK-CXL as adjuvant treatment

Case Report: Four eyes with corneal ulcer underwent PACK-CXL with ultraviolet-A rays and transepithelial riboflavin according to Dresden procedure. Preoperative and postoperative slit lamp examination of cornea and visual acuity assessment was done. Postoperative outcome includes objective signs like improvement in epithelialization, corneal scarring and vascularization.

Result: Three eyes healed completely with scarring at 1-month follow-up. One of the patients developed desemetocoele in 12 days. Epithelial defect completely healed over time but one underwent amniotic membrane transplant. Responded to treatment were defined by epithelialization and scar formation.

Conclusion: The corneal cross-linking has a beneficial role as an adjuvant therapy for corneal ulcer. It helps in relief of pain and healing of ulcer. PACK-CXL can be a choice of adjuvant treatment if the corneal ulcer doesn't heal using topical treatment.

Keywords: corneal cross-linking, corneal ulcer, clinical outcome

INTRODUCTION

Corneal ulcers are one of the most common eye diseases and cause morbidity, especially in developing countries. Corneal ulcers are also one of the leading causes of blindness worldwide. Corneal ulcers can be caused by bacteria, viruses, fungi, protozoa, and parasites. The risk factors for corneal ulcers are trauma, contact lens, history of surgery, history of ocular surface disease, dry eye, eyelid deformity, impaired corneal sensation, chronic use of topical steroids and immunocompromised patients.^{1,2}

Mainstay therapy for corneal ulcers currently was corneal topical antibiotics. Delayed diagnosis and initiation of antimicrobial treatment in corneal ulcers results in decreased therapeutic success rates. The emergence of multidrug-resistant bacteria is one of the reasons that complicates the treatment and cure of infectious keratitis.^{1,3}

Corneal cross-linking (CXL) is a new adjuvant treatment using ultraviolet A (UV-A) and riboflavin (Vit. B2) light to improve biomechanical binding to the corneal stroma. Photo Activated Chromophore for Keratitis - Corneal Cross-Linking (PACK-CXL) is an adjuvant treatment development for corneal ulcers that didn't have good response for antimicrobial alone. PACK-CXL is considered to have many mechanisms of action, one of which is inactivation of pathogens by directly damaging bacterial nucleic acids. Another advantage of PACK-CXL is its toxic effect on inflammatory cells which can limit the inflammatory response in infectious organisms. This case series will discuss PACK-CXL as an adjuvant therapy for corneal ulcers.^{4,5}

CASE SERIES

• Case number 1

A 22-year-old woman came to hospital with white spots in his left eye since 1 month ago. The patient had discharge from the eye in the morning, blurry and a feeling of lump in the eye without any pain. Initially, the patient complained recurrent red eyes 8 months ago after using eye drops herbal medicine, then the red eyes were felt worsen. Scraping examination from ophthalmologist in Jakarta displayed *Staphylococcus epidermidis* infection. Any surgical history was denied by the patient.

Ophthalmological examination revealed visual acuity in the right eye was 1.0 and the left eye was 1/300. Anterior segment examination of the left eye (Figure 1.A) showed ciliary injection of the conjunctiva. The cornea had ulcers measuring 5 x 6 x 2 mm, the sensibility test and anterior chamber was normal. The patient was diagnosed with a corneal ulcer ec staphylococcal OS. The therapy was started with moxifloxacin 1 drop/ hour, 1% cyclopentolate 3 drops/day, artificial tears 6 drops/day. The patient was then planned to undergo a PACK-CXL procedure.

The procedure started with septic and antiseptic procedure, then topical anaesthetic procedure was done using 0.5% pantocaine and pilocarpine. A wire speculum is used in the patient's eye. Riboflavin was dripped every 2 minutes for 15 minutes using riboflavin sodium phosphate 1 mg. UV-A irradiation of riboflavin was carried out every 3 minutes for 30 minutes. The final procedure of the patient was given a topical antibiotic ointment and contact lenses were inserted.

One week after the procedure, the patient had no complaints and felt that his vision was getting better. Ophthalmological examination revealed visual acuity of the left eye was 1/60. Examination of the anterior segment of the left eye (Figure 1.B) revealed ciliary injection. The cornea was cicatricial with neovascularization.

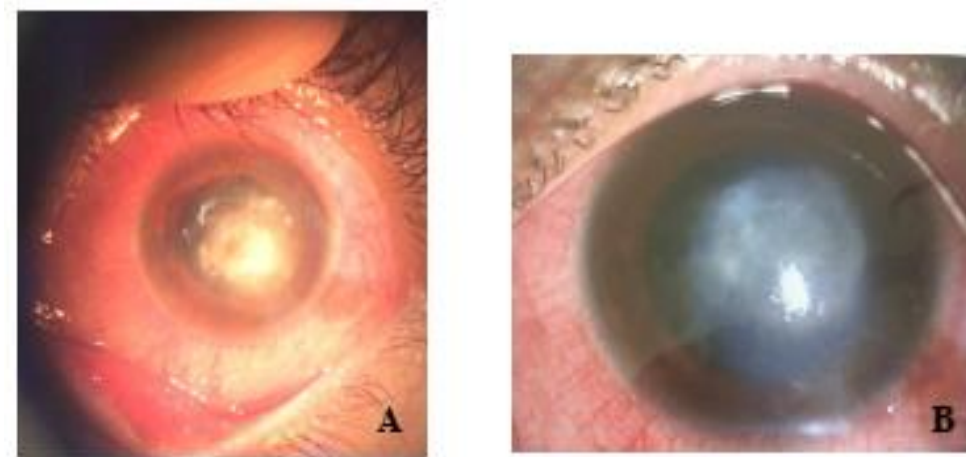


Figure 1. Images of slit lamps in the first case before and after the PACK-CXL action. A) Preoperative image. B) One week follow-up image after the PACK-CXL procedure. Corneal examination after PACK-CXL reveals no ulceration with development of less opaque cicatricial tissue.

Visual acuity in the left eye gradually increased to 0.16 F2 in the second week after the procedure. Examination of the anterior segment of the left eye showed no injection and there was cicatricial corneal scarring.

- **Case number 2**

A 50-year-old complaining red, itchy and blurry right eye which had been increasing since 1 month ago. No history of contact lens, trauma or gardening activities. The patient had diabetes mellitus and regularly takes metformin 3x500 mg. The patient went to an ophthalmologist in Ciamis and was given itraconazole and natamycin and was referred to Cicendo Hospital.

Ophthalmological examination revealed visual acuity in the right eye fixed at 1/300 and the left eye fixed at 0.5F1. Examination of eye pressure using Non-Contact Tonometry (NCT) in the right eye was undetected while in the left eye 13. Examination of the anterior segment of the right eye revealed protective ptosis, and ciliary injection of the conjunctiva was obtained. The cornea had ulcer measuring 6x5x2 mm, the anterior chamber of the eye had Van Herrick Grade III, flares and +4/+4 cells and there was hypopyon 2 mm, the pupil was round, the light reflex was ++ and the lens was clear (Figure 2.A). Corneal scraping showed gram (+) coccobacilli in two-by-two arrangement of 2-6 low power field (LPF). Leukocyte count was 10-15/LPF. Epithelial number was 5-7/LPF, no acanthamoeba and fungi were found. The patient was then diagnosed with corneal ulcer cum hypopyon gram (+) coccobacilli OD. Then the patient was planned to receive PACK CXL on her right eye.

Three days later the patient complained of watery eyes and reduced pain. Ophthalmological examination revealed visual acuity of hand movement in the right eye and 0.8 in the left eye. Examination of the anterior segment of the right eye revealed blepharospasm, ciliary injection of the conjunctiva. Cornea was edematous, ulcer was 4.8 x 4 mm, flare and cells +3/+3, and the lens was slightly cloudy (Figure 2.B). The patient got moxifloxacin 1 drop/hour, 1% cyclopentolate 3 drops/day and artificial tears 6 drops/day.

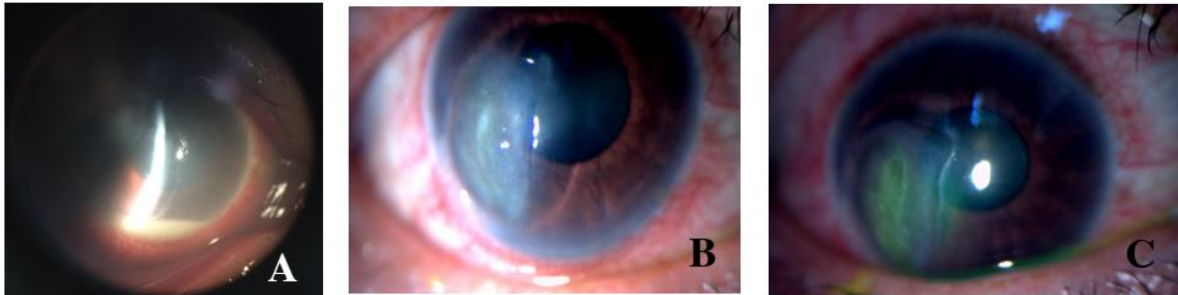


Figure 2. Image of slit lamp in the second case before and after PACK-CXL action. A) Preoperative image. B) 3-day follow-up image after the PACK-CXL procedure. C) 1-week follow-up image after the PACK-CXL procedure. It can be seen that injection and hypopyon was reduced, along with healing of ulcer and development of corneal scarring.

One week after the procedure patient still complained of watery eyes but no pain. Ophthalmological examination revealed visual acuity in the right eye was 0.08 and improved to 0.25 with pinhole and left eye fixed at 0.8 with pinhole. Examination of the anterior segment of the right eye revealed blepharospasm, ciliary injection of the conjunctiva. Cornea was cicatricial, fluorescein test (FT) was positive, ulcer size was 1 x 1.5mm, superficial punctate keratitis (KPS) was positive and keratic precipitates (KP), anterior chamber of the eye was Van Herick Grade III, flare and cell +1/+1 and the lens was slightly cloudy(Figure 2.C).

Watery eyes still complained by the patient 2 weeks after the procedure. Ophthalmological examination revealed visual acuity in the right eye was 0.1 improved with pinhole 0.32. Examination of the anterior segment of the right eye revealed blepharospasm, minimal ciliary injection of the conjunctiva. Cornea had cicatricial, FT (+) obtained KPS (+), KP (+), and pooling. The anterior chamber of the eye had Van Herrick Grade III, flares and cells -/-, and the lens was slightly cloudy. The patient was given moxifloxacin 8 drops/day, 1% cyclopentolate 3 drops/day and artificial tears 6 drops/day and also referred back to the RSUD Ciamis.

- **Case number 3**

A 66-year-old man complaining of redness and a white spot in the middle of the patient's left eye since 4 months ago, currently complaining of pain, watering and numbness in the left eye. The patient had a history of exposure to grass in his left eye. The patient had gone to an ophthalmologist at As-Syifa Hospital Bengkulu and was given levofloxacin 1 drop/hour, natamycin 1 drop/hour and 1% cyclopentolate drops/day.

Ophthalmological examination revealed visual acuity in the right eye fixed at 0.4 and the left eye close to face finger counting (CFFC). Examination of the anterior segment of the left eye revealed ciliary injection of the conjunctiva. Cornea had edema, infiltrates and FT (+) ulcer measuring 5 x 3.7 mm. The anterior chamber of the eye was found to be Van Herick Grade III, no flare and cells, round pupils, +/+ light reflex and slightly cloudy lens (Figure 3.A). The patient underwent scraping examination with the results gram (+) coccus 0-1/LPF, leukocyte count was <5/LPF, epithelial number was 0-1/LPF, slender fungal hyphae, septates and spores were found.

Patient diagnosed with corneal ulcer ec. mixed infection (gram (+) coccus and fungus) OS. Treatment was initiated with moxifloxacin 1 drop/hour, 1% cyclopentolate 3 drops/day, artificial tears 6 drops/day, natamycin 1 drop/hour and oral ketoconazole 2x300mg. Ketokonazole given 2x300 mg to reached maximal dosage per day which was 600 mg. Then the patient was planned to have a PACK-CXL procedure on his left eye.

Three days after the PACK-CXL procedure the patient complained of pain in the left eye. Ophthalmological examination revealed visual acuity of the left eye fixed at 1/60. Examination of the anterior segment of the left eye revealed ciliary injection of the conjunctiva. Cornea had ulcer measuring 3.4 x 2.1 mm. The anterior chamber of the eye had Van Herrick Grade III, flare and +2/+2 cells, round pupils, +/+ light reflex and slightly cloudy lens.

The patient then complained of pain, glare, itching and a feeling of lump in the left eye 7 days following the procedure. Ophthalmological examination revealed visual acuity of the left eye fixed at 1/60. Examination of the anterior segment of the left eye revealed ciliary injection of the conjunctiva. Cornea had ulcer measuring 2 x 2 mm, cicatricial, edematous and Descemet's folds. The anterior chamber of the eye was found to be Van Herrick Grade III, flare and cell -/-, round pupil, +/+ light reflex and slightly cloudy lens (Figure 3.B)

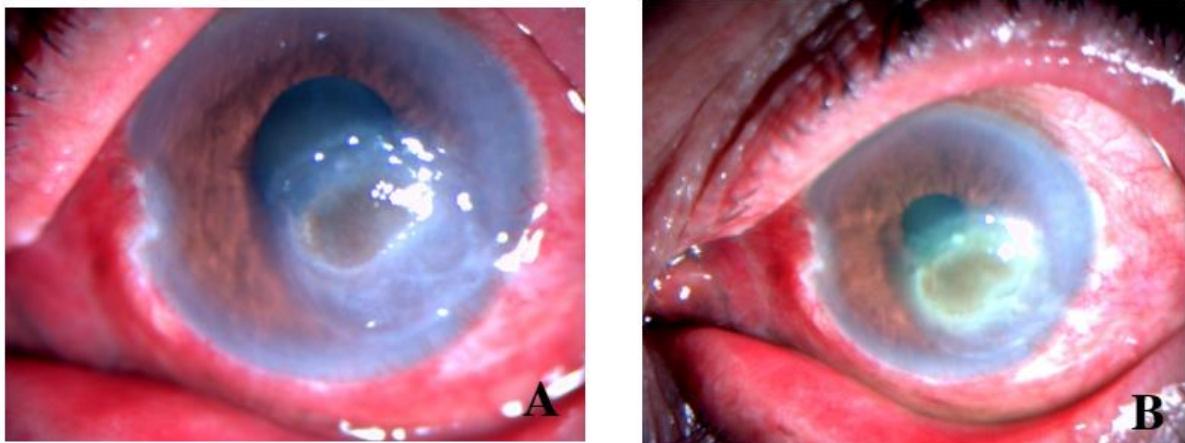


Figure 3. Image of slit lamps in the third case before and after the PACK-CXL action. A) Preoperative image. B) 1-week follow-up image after the PACK-CXL procedure. After PACK-CXL procedure, the cornea was cicatricial.

Two weeks after the procedure the patient had no complaints. Ophthalmological examination of the left eye revealed visual acuity fixed at CFFC. Ciliary injection of the conjunctiva was still found. Cornea had ulcer measuring 3.2 x 2 mm, cicatricial and edematous. The anterior chamber of the eye was found to be Van Herrick Grade III, flare and cell -/-, round pupil, negative synechiae, +/+ light reflex and slightly cloudy lens. The patient was diagnosed with improving corneal ulcer OS ec mixed infection + hypertension. The treatment was changed to levofloxacin 1 drop/hour and the remaining was still similar. The patient also got consulted to internal medicine for the management of hypertension.

- **Case number 4**

A 44-year-old man came with a history of foreign body two months ago, currently patient was complaining of pain and redness in the right eye. The patient went to an ophthalmologist at Garut Hospital and was given antifungal and antibiotic treatment. The patient was diagnosed of corneal ulcer cum hypopyon OD. On ophthalmological examination, visual acuity in the right eye and left eye was 0.8 improved to 1.0 with pinhole. Examination of the anterior segment of the right eye revealed protective ptosis of the eyelids. Cornea contained ulcer measuring 8x5 mm. The anterior chamber of the eye was found to be Van Herrick Grade III, hypopyon was 2 mm (Figure 4.A). Corneal scraping revealed gram (+) coccus one-on-one appearance 0-1/LPF, leukocyte count was <5/LPF, epithelial number was 0-1/LPF, oval septate fungal hyphae were found and no acanthamoeba were found. Ultrasound examination with the results of mild vitreous opacity ec vitreous fibrosis dd/inflammatory cells. The patient was then

diagnosed with corneal ulcer cum hypopyon ec mixed infection (gram (+) positive coccus and fungus) OD. The patient was treated with moxifloxacin 1 drop/hour, cyclopentolate 1% 3 drops/day, artificial tears 6 drops/day, natamycin 1 drop/day and oral ketoconazole 2 x 300 mg. Then the patient was planned to undergo a PACK-CXL OD procedure on his right eye.

Three days after the procedure patient complained of a feeling of lump and glare in the right eye. Ophthalmological examination revealed visual acuity in the right eye fixed at CFFC. Examination of the anterior segment of the right eye revealed ciliary injection of the conjunctiva. Cornea contained ulcer measuring 6.7x4 mm. The anterior chamber of the eye was found to be Van Herrick Grade III and hypopyon was 1 mm high (Figure 4.B). The patient was diagnosed with corneal ulcer cum hypopyon ec mixed infection OD. The patient was treated with moxifloxacin 1 drop/hour, natamycin one drop/hour, cyclopentolate 1% 3 drops/day, artificial tears 6 drops/day and oral ketoconazole 2 x 300 mg.

1 week after the PACK-CXL procedure during the examination the patient complained that the pain had decreased but his vision was getting blurry. Ophthalmological examination revealed visual acuity in the right eye fixed at 1/300. Examination of the anterior segment of the right eye revealed protective ptosis, ciliary injection of the conjunctiva. Cornea contained ulcer measuring 6x4 mm. The anterior chamber of the eye was found to be Van Herrick Grade III, hypopyonic plaques (+) (Figure 4.C). The patient was diagnosed with corneal ulcer cum hypopyon ec mixed infection OD. The patient was treated with levofloxacin 1 drop/hour, natamycin 1 drop/hour, 1% cyclopentolate 3 drops/day, artificial tears 6 drops/day and oral ketoconazole 2 x 300 mg. The patient was planned for debridement + Anterior chamber washout + single layer AMG + intracamera and intrastromal injection of fluconazole OD.

One week after the procedure the patient complained of reduced pain but blurred vision. On ophthalmological examination, the visual acuity of the right eye fixed at CFFC. Examination of the anterior segment of the right eye revealed blepharospasm, ciliary injection of the conjunctiva. The cornea had intact suture and grafts. The patient was diagnosed with Post debridement + washout AC + single layer Amnion Membrane Graft (AMG) + intracamera and intrastromal injection of fluconazole OD on indication of corneal ulcer cum hypopyon OD ec mixed infection. The prior regimen therapy was given to the patient.

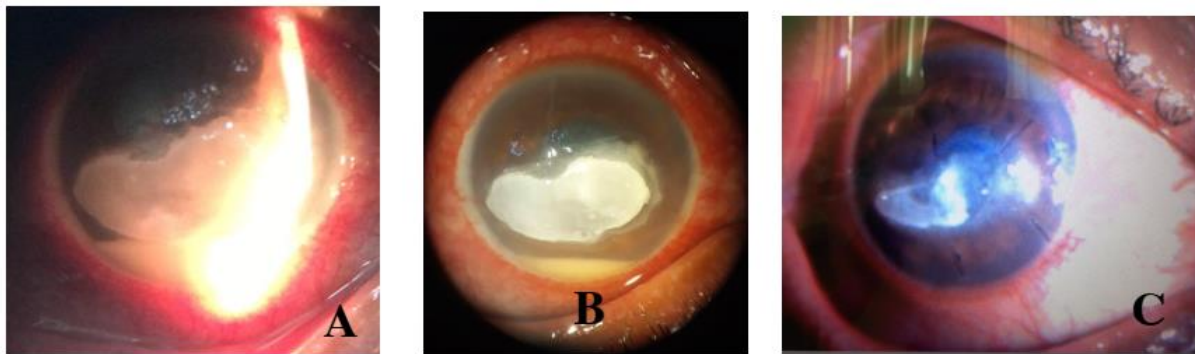


Figure 4. Image of slit lamps in the fourth case before and after the PACK-CXL procedure. A) Preoperative image. B) 3 days follow-up image of after the PACK-CXL procedure. C) 1- week follow-up image after PACK-CXL+ Post debridement + AC washout + single layer AMG + intracamera and intrastromal injection of fluconazole OD. PACK-CXL procedure alone did not yield positive clinical outcome, therefore the combination with AMG helped produce the desired outcome of ulceration healing and cicatricial cornea.

Two weeks later the right eye visual acuity fixed at CFFC. Examination of the anterior segment of the right eye revealed minimal ciliary injection in the conjunctiva. The cornea had intact suture and grafts. Levofloxacin and natamycin was changed to 8 drops/day. Other therapies were still the same as the previous therapeutic regimen, then the patient was referred back to Garut Hospital.

DISCUSSION

Corneal ulcer is a disease characterized by the presence of infiltrates in the cornea and damage to the corneal layer so that it can threaten vision. Corneal ulcer reduce the integrity and binding of the corneal stroma. Conventional treatment of corneal ulcer is based on topical administration of antibiotics, antifungal, and other antimicrobial agent. The provision of topical treatment had many limitations such as the large variety of drugs, inadequate penetration of the drug in the ulcer and is influenced by patient compliance in drug use. Therefore, treatment and other adjuvant treatments are needed.^{6,7}

Patient and ulcer characteristics described in table 1, show that of the 4 patients, the mean age of the patients was 45.5 years with an age range of 20-70 years. The duration of time from the onset of symptoms to the time the patient came to Cicendo Hospital was 3.75 months. The ulcer grading in patients using the Jones Criteria was moderate to severe, assessing by the size of the ulcer more than 6 mm in diameter, ulcer depth in 1/3 of the corneal layer and rapid disease progression. The patient's visual acuity on arrival ranged from 1/300 - CFFC. The results of scraping on patients indicated the cause of ulcer by gram (+) coccus and fungi.^{8,9}

Table 1. Initial patient and ulcer characteristics

Case	Age/Gender	Duration (months)	Eye Affected	VA (initial examination)	Ulcer size (mm x mm)	Grams	KOH
1	22/F	8	OS	1/300	5x6	GPC	-
2	50/F	1	OD	1/300	6x5	GPC	-
3	66/M	4	OS	0.5/60	5x3.7	GPC	+
4	44/M	2	OD	1/300	8x5	GPC	+

F: Female, M: Male, OS: Oculi sinistra, OD: Oculi dextra, VA: Visual acuity, GPC: Gram Positive Cocci

PACK-CXL is a therapeutic development for corneal ulcer. PACK-CXL is considered to have many mechanisms of action, one of which is inactivation of pathogens by directly damaging bacterial deoxyribonucleic acid. As shown in table 2, in this case series the patients with only gram-positive stains experienced better wound development. Other studies have shown good results in bacterial keratitis but in other types of keratitis have mixed results.^{10,11}

Table 2. Visual Acuity after PACK-CXL procedure

Case	Preoperative VA	3 days control	1-week control	2-weeks control	Clinical Outcome
1	1/300	CFFC	1/60	0,16f2	Healed (+) Scarring
2	1/300	1/300	0.08 ph 0.25	0,1 ph 0,32	Healed (+) Scarring
3	0.5/60	1/60	1/60	0,5/60	Healed (+) Scarring
4	1/300	1/300	0.5/60	0,5/60	Ulcer (+)

Two patients in this case series had an increase in visual acuity (VA) and 2 patients did not experience an increase in VA. The study by Cecilia et al also found no correlation between increased VA in PACK-CXL cases. However, patients diagnosed with fungal corneal ulcer had decreased visual acuity, corresponding to cases 3 and 4 in this case series.^{12,13}

The function of PACK-CXL for the treatment of fungal keratitis is still debated. Vadim et al stated that the use of PACK-CXL in fungal keratitis can reduce the melting progression of the cornea so that the next step is keratoplasty. The combination of PACK-CXL and keratoplasty aims to maintain eyeball shape and visual function in patients. This is in accordance with case number four where the patient had a corneal ulcer with gram staining and KOH (+), so the patient underwent PACK-CXL action. One week after the PACK-CXL

procedure, the ulcer was found to be persistent, so AMG was performed. One week follow-up post AMG action the ulcer closed with an increase in vision in the patient. Limitation of the study were this was a case series that represent level IV evidence in the hierarchy of evidence. As a result of the absence of control participants, case series were liable to bias.^{14,15}

CONCLUSION

PACK-CXL can be a choice for adjuvant treatment if the corneal ulcer cannot be treated using topical treatment. Corneal ulcer with bacterial causes give better results in terms of tissue healing and improvement of visual acuity. Corneal ulcer with fungal causes still require further research on PACK-CXL response to tissue healing and visual acuity. PACK-CXL can be used as adjuvant therapy in corneal ulcer with fungal causes before other procedures are performed.

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