Case report

Long-term outcomes of riboflavin photodynamic antimicrobial therapy as a treatment for infectious keratitis

Jaime D. Martineza,b,1, Alejandro Arboledab,1, Andrea Naranjoa,b, Mariela C. Aguilarb, Heather Durkee b, Pedro Monsalve a,e, Sander R. Dubovy a,d,e, Kendall E. Donaldson a, Darlene Miller a,c, Guillermo Amescua a,b,∗, Jean-Marie Parela,b,f

a Anne Bates Leach Eye Hospital, Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA
b Ophthalmic Biophysics Center, Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA
c Ocular Microbiology Laboratory, Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA
d Florida Lions Ocular Pathology Laboratory, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA
e Ophthalmic Biophysics Center, Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA
f Department of Pathology, University of Miami, University of Miami Miller School of Medicine, Miami, FL, USA

ARTICLE INFO

Keywords:
Corneal infectious keratitis
Photodynamic antimicrobial therapy
Crosslinking
Riboflavin

ABSTRACT

Purpose: To report the long-term outcomes of three patients with infectious keratitis treated with riboflavin photodynamic antimicrobial therapy (PDAT).

Observations: Case series reporting three patients with infectious keratitis unresponsive to standard medical treatment who underwent riboflavin photodynamic antimicrobial therapy (PDAT) as an adjunct therapy. One male and two female patients were treated, the median age of presentation was 58 years (range, 29–79 years). The organisms isolated and treated were Pseudomonas aeruginosa, Mycobacterium cheloneiae, and Curvularia spp. Different risk factors to develop corneal infection ulcers were identified, including corneal abrasion in a contact lens user, history of penetrating keratoplasty with chronic use of topical corticosteroids, and organic trauma. The median follow-up was 47 months (range 37–54 months), and there were no complications secondary to riboflavin PDAT treatment. Two cases underwent optical penetrating keratoplasty after infection was resolved and ocular surface was quiet for at least 3 years.

Conclusions and importance: Riboflavin PDAT can be used as an adjunct treatment in infectious keratitis to strengthen the corneal collagen fibers, delay keratolysis, and allow more time for antimicrobials to work and this way prevent a corneal perforation.

1. Introduction

Even with proper medical management, some cases of infectious keratitis can progress to a corneal perforation. In some of these cases, a therapeutic corneal transplant is required. However, performing a corneal transplant on an infected and inflamed ocular surface increases the risk of graft failure or graft rejection.1

Corneal crosslinking with riboflavin and ultraviolet-A (UV-A) light has been established as a first-line treatment to prevent the progression of keratoconjunctival or corneal ectasias by strengthening the corneal collagen fibers.2 It was later proposed as a treatment for infectious keratitis unresponsive to medical treatment and was described in the literature as photoactivated chromophore (PACK-CXL)3–4 or riboflavin Photodynamic Antimicrobial Therapy (PDAT).5–6 Bamdad et al. reported a randomized control trial in which the group treated with PACK-CXL had a shorter course of medical treatment and decreased need for therapeutic corneal transplantation.7 A few articles have reported the use of riboflavin CXL as an adjunct therapy for Pseudomonas keratitis8–10 and Mycobacterium keratitis,11,12 but none have reported its utility in treating Curvularia spp.

We present three cases of infectious keratitis that presented to Bascom Palmer Eye Institute and were treated with riboflavin PDAT. Informed consent was obtained, and the procedure was performed following a modified Dresden protocol.2 Under topical anesthesia,
corneal ulcer scraping was performed 1–2 mm around the corneal epithelial defect. One drop of 0.1% riboflavin in 20% dextran solution was applied to the cornea every 3 minutes for a total of 30 minutes. A custom-made shield was placed over the limbal area for protection and the cornea was irradiated for 30 minutes with a custom-made ultra-violet-A (UV-A) light source for a radiant exposure of 5.4 J/cm². (Fig. 1). The light source, previously described by Halili et al., who conducted in vitro experiments with multiple organisms, contains twenty-four 375nm LEDs and emits a power density of 3 mW/cm².6

2. Findings

2.1. Case 1

A 29-year-old female was referred to our institution with a corneal ulcer secondary to a corneal abrasion while removing a soft contact lens from her right eye. Corneal ulcer cultures came back positive for Pseudomonas aeruginosa with S-/U+ genotype which did not respond to standard medical treatment for 15 days (Table 1 and Fig. 2A). The patient underwent riboflavin PDAT with placement of an amniotic membrane (Ambrodisk, Costa Mesa, CA, USA) and bandage contact lens following the procedure. Topical moxifloxacin with Doxycline and Vitamin C was continued, while the patient started tapering prednisolone acetate.

The patient significantly improved after 2 weeks of riboflavin PDAT (Fig. 2 B). Two months after PDAT, antibiotic treatment was suspended. One year after PDAT, the best corrected visual acuity (BCVA) was 20/800, and examination revealed a vascularized and opacified cornea with complete epithelialization and quiet conjunctiva without hyperemia (Fig. 2C). Fifteen months after riboflavin PDAT treatment, we proceeded with an optical penetrating keratoplasty (PK) followed by amniotic membrane placement without complications (Fig. 2D and E). Four years and 6 months after the riboflavin PDAT procedure, BCVA was 20/30, IOP was 20 mmHg, and the corneal graft remained clear without signs of rejection or infection. (Fig. 2F).

2.2. Case 2

A 79-year-old female patient with history of PK secondary to Fuchs corneal dystrophy 13 years prior, presented with left eye progressive infectious keratitis in the left eye presumed to be secondary to a loose suture. Corneal ulcer cultures came back positive for Mycobacterium chenolae sensitive to Clarithromycin and with intermediate sensitivity to Amikacin (Table 1 and Fig. 3A). There was no improvement in the following 7 days on standard medical treatment and the decision to undergo riboflavin PDAT was made due to the presence of progressive keratolysis. After PDAT, she was started on 0.5% Cyclosporine drops 4 times a day. Nine days after PDAT, the BCVA was 20/200, there was decreased conjunctival hyperemia, and the epithelial defect had healed (Fig. 3B). Three years after riboflavin PDAT, the patient continued on acetate prednisolone eye drops once a day, her BCVA was 20/40 and IOP was 19 mmHg. Slit-lamp examination showed a quiet conjunctiva, clear corneal graft and IOL in place (Fig. 3C).

2.3. Case 3

A 58-year-old male presented with a corneal ulcer in the right eye caused by injury while cutting a tree branch. Corneal ulcer cultures came back positive for Curvularia spp. The patient was started on Natamycin every hour and 0.5% Moxifloxacin every 4 hours (Table 1 and Fig. 4 A). After 15 days without clinical improvement and due to rapid progression of the stromal necrosis, the patient underwent riboflavin PDAT. After treatment, the medication regimen was: Natamycin eye drops every 2 hours, 200 mg Fluconazole tablets twice a day, Cyclosporine-A eye drops 4 times a day, Atropine once a day, and Moxifloxacin (Fig. 4B). After 2 months, the corneal infiltrate disappeared.
but evidence of deep stromal neovascularization was found (Fig. 4C). Topical and systemic antifungal medications were discontinued. Six months after riboflavin PDAT, the patient’s visual acuity was 20/800 with moderate corneal scarring in the visual axis, a cataract, and iris synechiae (Fig. 4D). Finally, the patient underwent cataract surgery and intraocular lens placement without complications. Four months after surgery, BCVA was 20/70, but the patient complained of severe glare. An optical PK and pupilloplasty was performed (Fig. 4 E, and F). Three years and 5 months after riboflavin PDAT, BCVA was 20/70, IOP was 16 mmHg, and the corneal graft remained clear with no signs of rejection or infection.

3. Discussion

Infectious keratitis is a challenging disease, where the causative organisms may display unpredictable behavior and resistance to standard medical treatment. Furthermore, complications that arise from the resistance to topical antimicrobials can lead to devastating consequences. The patients in this study exhibited risk factors of infectious keratitis: contact lens use, prior corneal surgery, and prolonged steroid use.

Over the last decade, attempts have been made to treat refractory cases of infectious keratitis with new medications and technologies, one such being PACK-CXL. Both in vitro and in vivo studies have shown microbial inhibition of Pseudomonas aeruginosa, Mycobacterium chelonae, and filamentous fungi with CXL treatment.

Curvularia spp. is a rare cause of fungal keratitis in the United States, however, there has been an increase of in the number of cases reported in our institution. In the case reported, the patient progressed to stromal necrosis despite compliance to standard medical treatment. Other cases have either responded to standard medical treatment, required a therapeutic penetrating keratoplasty, or have been treated for endophthalmitis.

Studies have shown that the adjunct effect of antibiotics and CXL is greater in treating infections than antibiotics alone or CXL alone. The patients in our study may be benefitting from this finding, and the marked improvement after PDAT may be due to the synergistic effect of the light therapy and medications. Given the aggressive nature of the microorganisms and the advanced stage of the infections, adjunct treatment was offered to the patients to provide the most effective

Fig. 2. Case 1. (A) Slit-lamp photograph of the right eye with corneal melting inferiorly and thinning. (B) two weeks after riboflavin PDAT, presenting with central corneal infiltrate shrinkage more than 50% and increased peripheral corneal neovascularization. (C) One year after riboflavin PDAT, no corneal infiltration or diffuse corneal scarring were observed. (D) Optical penetrating keratoplasty (OPK) was done one year after PDAT. (E) No organisms identified on gram stained section of cornea. Brown and Hopps gram stain, 400X. (F) OPK remains clear on last follow-up . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
treatment. Studies by Said et al. and Kasetswan et al., showed that PACK-CXL reduced late complications such as corneal perforation or recurrence of infection compared to antibiotic treatment alone.2, 4, 21 Moreover, Bamdad et al. demonstrated a faster recovery of epithelial defect and infiltrates with PACK-CXL.22 Zamani et al. reported 8 patients diagnosed with Pseudomonas aeruginosa keratitis who did not respond to standard antimicrobial treatment; however, after riboavin PDAT was performed. Shortly after PDAT, patients improved both subjectively and objectively, reporting less pain and appearing better on slit lamp exam. Our presented cases have a significant longer follow up after riboavin PDAT compared to reported cases in the literature.

All three patients treated with riboavin PDAT had a good long-term outcome with no complications. A potential explanation for this may be increased resistance of corneal tissue to enzymatic digestion following PDAT. This enhances corneal strength, delays corneal melting, and allows time for the antimicrobials to take effect.23 Further studies should be performed to better understand the changes of tissues following PDAT.

In summary, the cases presented highlight the use of riboavin PDAT as an adjunct treatment for infectious keratitis, with good long-term outcome. Even in the setting of thin corneas, this treatment can help prevent a perforation that would normally result in a therapeutic corneal transplant. Although results are encouraging, and the patients presented had favorable outcomes, we understand the limitations of a retrospective study. Prospective controlled clinical trials are needed to confirm the effectiveness of Riboavin PDAT in severe cases of infectious keratitis.

4. Patient consent

The project was deemed to meet criteria for a case series by the University of Miami Institutional Review Boards (IRB). Therefore, no IRB submission was required prior to reviewing the cases. The study was conducted in accordance with the principles of the Declaration of Helsinki. Patients in this series provided signed voluntary and informed consent to the described treatment. Patients in this series displayed appropriate capacity to provide consent. Patients understood the risks, benefits, and alternatives for the riboavin photodynamic antimicrobial therapy and understood they were entitled to withdraw previous consent at any time during the treatment. Consent to publish the case series was not obtained from the patients. The case series does not contain any identifying information.

Funding

Supported in part by Edward D. and Janet K. Robson Foundation (Tulsa, OK), Florida Lions Eye Bank and the Beauty of Sight Foundation (Miami, FL), Drs. K. R. Olsen and M. E. Hildebrandt, Drs. Raksha Urs, and Aaron Hurtado, NIH Center Grant P30EY14801, Research to Prevent Blindness, Henri and Flore Lesieur Foundation (Chicago, IL) (J.-M. Parel). Research to Prevent Blindness, the Pan-American Association of Ophthalmology and Retina Research Foundation (J. D. Martinez).

Conflicts of interest

None of the authors have financial disclosures.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Acknowledgments

The authors of this study would like to thank Jennifer Phu for her help preparing the patients and coordinating the treatments. Cynthia Maza from the Florida Lions Ocular Pathology laboratory for helping with histopathology. Harry W. Flynn, MD for following patients, Cornelis Rowaan, BS, Alex Gonzalez, BA, and Wilam Lee of the Ophthalmic Biophysics Center for participating to the design, development, and construction of the UVA irradiation source, Xiao-Yi Zhou MD and Cynthia Maza, from the Florida Lions Ocular Pathology laboratory for helping with histopathology.

References

1. Hosein P, et al. Emergency corneal grafting in the UK: a 6-year analysis of the UK Transplant Registry. Br J Ophthalmol. 2018;102(1):26–30.
2. Wollensak G, Spoerl E, Seiler T. Riboavin/ultraviolet-A-induced collagen cross-linking for the treatment of keratoconus. Am J Ophthalmol. 2003;135(5):620–627.
3. Price MO, Price Jr FW. Corneal cross-linking in the treatment of corneal ulcers. Curr Opin Ophthalmol. 2016;27(3):250–255.
4. Said DG, et al. Collagen cross-linking with photoactivated riboflavin (PACK-CXL) for the treatment of advanced infectious keratitis with corneal melting. Ophthalmology. 2014;121(7):1377–1382.
5. Arboleda A, et al. Assessment of rose bengal versus riboavin photodynamic therapy for inhibition of fungal keratitis isolates. Am J Ophthalmol. 2014;158(1):64–70 e2.
6. Halli F, et al. Rose bengal- and riboavin-mediated photodynamic therapy to inhibit methicillin-resistant Staphylococcus aureus keratitis isolates. Am J Ophthalmol. 2016;166:194–202.
7. Bamdad S, Malekhosseini H, Khozravi A. Ultraviolet A/riboavin collagen cross-linking for treatment of moderate bacterial corneal ulcers. Cornea. 2015;34(4):402-406.
8. Price MO, et al. Photoactivated riboflavin treatment of infectious keratitis using collagen cross-linking technology. J Refract Surg. 2012;28(10):706–713.
9. Shetty R, et al. Collagen cross-linking in the management of advanced non-resolving microbial keratitis. Br J Ophthalmol. 2014;98(8):1033–1035.
10. Mattila JS, et al. Treatment of Pseudomonas aeruginosa keratitis with combined corneal cross-linking and human amniotic membrane transplantation. Acta Ophthalmol. 2013;91(5):e410–e411.
11. Alio JL, et al. Corneal cross-linking and infectious keratitis: a systematic review with a meta-analysis of reported cases. J Ophthalmic Inflamm Infect. 2013;3(1):47.
12. Iseli HP, et al. Ultraviolet A/riboavin corneal cross-linking for infectious keratitis associated with corneal melts. Cornea. 2008;27(5):590–594.
13. Augustin DK, et al. Role of defensins in corneal epithelial barrier function against Pseudomonas aeruginosa traversal. Infect Immun. 2011;79(2):595–605.
14. Martinez JD, et al. Bilateral Curvularia keratitis: using confocal laser scanning microscopy on an ex vivo human corneal model. Cornea. 2015;34(10):1276–1280.
15. Klein BB, et al. Curvularia endophthalmitis. Ophthalmology. 2001;98:111–130 discussion 130-2.
16. Makdoumi K, et al. Evaluation of antibacterial efficacy of photo-activated riboflavin using ultraviolet light (UVA). Gryafes Arch Clin Exp Ophthalmol. 2010;248(2):207–212.
17. Canas CB, et al. Microbiologic, pharmacokinetic, and clinical effects of corneal collagen cross-linking on experimentally induced Pseudomonas keratitis in rabbits. Cornea. 2015;34(10):1276–1280.
18. Schrier AJ, et al. In vitro antimicrobial efficacy of riboflavin and ultraviolet light on Staphylococcus aureus, methicillin-resistant Staphylococcus aureus, and Pseudomonas aeruginosa. J Refract Surg. 2009;25(9):S799–S802.
19. Alshehri JM, et al. Evaluation of corneal cross-linking for treatment of fungal keratitis: using confocal laser scanning microscopy on an ex vivo human corneal model. Invest Ophthalmol Vis Sci. 2016;57(14):16367–16374.
20. Ashvin Reddy AR, Miller Darlene, Flynn Harry, Smiddy William, Lara Willfredo, Albini Thomas. The incidence of Curvularia keratitis and A case series of Curvularia endophthalmitis. Invest Ophthalmol Vis Sci. 2013;54(15):1162.
21. Kasetswan N, Reintrepayoon U, Sattipitaksul V. Photoactivated chromophore for moderate to severe infectious keratitis as an adjunct therapy: a randomized controlled trial. Am J Ophthalmol. 2016;165:94–99.
22. Zamani M, Panahi-Bazar M, Ansadi M. Corneal collagen cross-linking for treatment of non-healing corneal ulcers. J Ophthalmic Vis Res. 2015;10(1):16–20.
23. Sachdev GS, Sachdev M. Recent advances in corneal collagen cross-linking. Indian J Ophthalmol. 2017;65(9):787–796.