Review Article

Riboflavin-UVA collagen cross-linking for the treatment of acanthamoeba keratitis

Choul Yong Park[1], Roy S. Chuck[2]

[1]Department of Ophthalmology, Dongguk University, Ilsan Hospital, Goyang, South Korea; [2]Department of Ophthalmology and Visual Sciences, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: CY Park; (IV) Collection and assembly of data: CY Park; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Choul Yong Park, MD, PhD. Department of Ophthalmology, Dongguk University, Ilsan Hospital, Donggukro 27, Ilsan-dong-gu, Goyang, Gyunggi-do, 10326, South Korea. Email: oph0112@gmail.com.

Abstract: In this review, recent studies regarding riboflavin-ultraviolet A (UVA) collagen cross-linking for the treatment of acanthamoeba keratitis (AK) were reviewed. English written studies about acanthamoeba, keratitis, riboflavin and collagen cross-linking were retrieved from PubMed search engine (www.ncbi.nlm.nih.gov/pubmed). Although there were significant numbers of cases reporting the effectiveness of riboflavin-UVA collagen cross-linking in AK, experimental studies (*in vivo* and *in vitro*) failed to verify amoebicidal or cysticidal effect of riboflavin-UVA collagen cross-linking. In conclusion, the efficacy of riboflavin-UVA collagen cross-linking for the treatment of AK is still debatable. It is necessary to conduct a prospective case-control study for clear guidance for clinicians.

Keywords: Acanthamoeba; keratitis; collagen; ultraviolet A (UVA); riboflavin; cross-linking

Received: 10 December 2018; Accepted: 26 January 2019; Published: 11 February 2019.

doi: 10.21037/aes.2019.01.06

View this article at: http://dx.doi.org/10.21037/aes.2019.01.06

Introduction

First reported in the U.S. and the U.K. in 1973 acanthamoeba keratitis (AK) is among the most intractable infectious diseases of the human cornea (1,2). The incidence of AK is widely variable and ranges from 0.15 per million in United States to 1.4 per million in United Kingdom (2). Contact lens use, trauma and exposure to contaminated water are the most common risk factors for AK (2). More than 85% of AK occurs in contact lens users, especially in countries where the prevalence of contact lens wear is high (2).

In general, early diagnosis and prompt delivery of effective antimicrobial agents is a key for successful treatment of infectious keratitis. Typically, AK is unilateral and progresses slowly. Therefore, the diagnosis of AK is usually delayed, unless there is keen awareness among clinicians (3,4). During the early phase of AK, the clinical feature is similar to other mild corneal diseases such as punctate epitheliopathy or pseudodendrites mimicking herpes keratitis (1). Since the toxicity of anti-Acanthamoeba medication is very strong, many are hesitant to begin treatment without clear diagnosis. In addition, the resistance of Acanthamoeba cysts to antimicrobial chemotherapy is another significant impediment to successful treatment (1,2,4).

Currently, the mainstay of AK treatment is combined use of two biguanides such as polyhexamethylene biguanide (PHMB) 0.02% to 0.06% and Chlorhexidine 0.02% to 0.2% (2,4). The action of biguanides is to damage the cytoplasmic membrane of Acanthamoeba and the inhibition of its respiratory enzymes (5). In European countries, commercial diamidine eyedrop [propamidine isethionate 0.1% (Brolene®)] is available for the treatment of AK. The mechanism of action of diamidines (hexamidine and propamidine) is to jeopardize DNA synthesis inside Acanthamoeba species by inhibiting S-adenosylmethionine decarboxylase (6).

Despite this regimen, there are many cases of AK treatment of failure, and novel treatment options are urgently needed (4).

Riboflavin-ultraviolet A (UVA) assisted corneal collagen cross-linking (CXL) has been widely used to enhance corneal mechanical strength in various ectatic corneal diseases such as keratoconus, pellucid marginal degeneration and progressive ectasia following photorefractive surgeries (7,8). The treatment is well established as a minimally invasive procedure to slow or halt progression of these diseases (8).

In addition to enhancing corneal mechanical strength, recent findings have revealed a novel treatment role of riboflavin-UVA CXL (9-12). Previous studies have repeatedly verified that riboflavin-UVA CXL is an effective treatment for infectious keratitis which is refractory to conventional topical antibiotic treatment. Reports of successful recovery from refractory fungal and amoebic keratitis after riboflavin-UVA CXL have been reported (11,13). Riboflavin-UVA CXL for the management of corneal infection is now known as PACK-CXL (photoactivated chromophore for keratitis-CXL) (14,15).

In this review, *in vivo* and *in vitro* evidence regarding the role of CXL in the treatment of AK is examined and summarized. In addition, a future direction of investigation is proposed.

Underlying mechanism of Riboflavin-UVA CXL in infectious keratitis

Riboflavin-UVA CXL was first introduced by researchers at the Technical University of Dresden, Germany in the early 1990s. Through a series of photochemical reactions such as photosensitization, photo-oxidation, and photopolymerization, UVA is thought to activates riboflavin and generate singlet oxygen, which then facilitates cross-linking between adjacent collagen fibrils in corneal stroma via various pathways such as imidazolone production, triggering of endogenous populations of carbonyl groups, and releasing free radicals from riboflavin (7). In detail, the underlying photochemical processes consist of both aerobic (Type II photochemical kinetic mechanism) and anaerobic (Type I photochemical kinetic mechanism) phases. The role of riboflavin is to act as a photosensitizer. It is activated by UVA to an excited singlet or reactive triplet state and interacts with triplet oxygen species in the atmosphere to generate active singlet oxygen (aerobic phase). Active singlet oxygen induces the crosslink between carbonyl groups of collagens. In the anaerobic phase, the oxygen depletion induces triplet riboflavin to form riboflavin free radicals such as 2,3-butanedione which interacts with corneal stroma and induces crosslinks between collagen molecules. Because the depth of penetration of UVA is limited, the typical increase in the diameter of type I collagen fibers is mainly confined to the anterior stromal layer.

CXL improves corneal resistance to proteolytic enzymes secreted by the microorganisms. The stiffening effect of CXL on the corneal stroma increasing the resistance of corneal tissue to enzymatic digestion combined with the toxic action against micro-organisms offers great promise for a possible role in the treatment of microbial keratitis (7). In the majority of intractable microbial keratitis cases reported, progression of the melting process was halted within a few days of treatment and emergency keratoplasty was avoided. There seems to be a consensus forming among ophthalmologists that riboflavin-UVA CXL is a novel and effective treatment modality for multi-drug resistant bacterial keratitis (15). However, the effect of riboflavin-UVA CXL on AK is still debatable. Interestingly, in a recent survey, more than half (52%) of clinical experts responded that riboflavin-UVA CXL is not effective in AK and may even be detrimental (15).

The safety of CXL has been extensively studied. UVA can be toxic to corneal endothelium, lens and macula. However, previous study has shown that riboflavin absorption of UVA prevents damaging UVA penetration to the corneal endothelium (16). Using an irradiance of 3 mW/cm^2 of UVA and 0.1% riboflavin, as much as 95% of UVA light is absorbed within the cornea before reaching the anterior chamber. This corneal UVA absorbance results in a 20-fold reduction of the original irradiance of 3 mW/cm^2 of UVA (at the corneal surface) down to 0.15 mW/cm^2 (at the endothelial level), which is below 0.36 mW/cm^2, the threshold considered cytotoxic for the endothelium (17,18).

There have been several treatment protocols developed for riboflavin-UVA CXL. The conventional Dresden protocol for CXL uses irradiance of either 3 mW/cm^2 or 5.4 J/cm^2 of 370 nm of UVA for 30 minutes after 30 minutes of instillation of 0.1% riboflavin in 20% dextran solution (19)]. The riboflavin solution is applied to the corneal surface every 3–5 minutes during UVA irradiation. As an alternative treatment, several accelerated CXL protocols were suggested based on the Bunsen-Roscoe law of photochemical reciprocity where the same photochemical effect has to be maintained while applying a higher irradiation dose for a shorter period of time (20). Most accelerated protocols treat the cornea using 9 to 30 mW/cm^2 of UVA irradiation for 3 to 10 minutes.

For example, current accelerated protocols use irradiance of 9 mW/cm^2 for 10 minutes, 18mW/cm^2 for 5 minutes and 30mW/cm^2 for 3 minutes in order to achieve a similar effect as Dresden protocol (20).

In vitro evidence of riboflavin-UVA CXL effect on AK

In vitro studies have shown that riboflavin and UVA (3 mW/cm^2 for 30 or 60 minutes) does not eradicate Acanthamoeba strains (21-23). Kashiwabuchi *et al.* observed no antitrophozoite (clinically isolated Acanthamoeba species) effect of riboflavin and UVA combination treatment *in vitro* and no improvement of clinical signs in AK animal model (Chinese hamster models) (22). del Buey *et al.* cultured two strains of Acanthamoeba (Acanthamoeba species 65 and 7376) on non-nutrient agar plates covered with *Escherichia coli* as a food source (21). They applied combined riboflavin and UVA treatment (5.4 and 10.8 J/cm^2, 370 nm, 30 or 60 minutes) to the central Acanthamoeba inoculation zone and measured the viability zone. They found live trophozoites and cysts were observed more than 5 mm away from the treatment center even at 24 hours after treatment, indicating no amoebicidal effect of the treatment. Berra *et al.* created AK in rabbit eyes and applied riboflavin-UVA CXL (3 mW/cm^2 for 30 minutes) for the treatment (23). They found that rabbits treated with CXL showed no significant clinical difference compared to the no-treatment control rabbits. Furthermore, the protozoa count was even higher in the CXL group than in the control group.

Although riboflavin and UVA treatment failed to show amoebacidal effect in previous studies, there was another report that another cross-linking photosensitizer, rose bengal, showed promising effect when green light irradiation was used. Atalay *et al.* applied rose bengal solution (0.1% or 0.2%) to culture wells containing Acanthamoeba with subsequent irradiation with green light (523 nm, 5.4 J/cm^2). Their interesting finding was that rose Bengal-green light CXL eradicated 66% of Acanthamoeba trophozoites. The control wells with riboflavin-UVA CXL showed no significant amoebicidal effect (24).

Clinical evidence of riboflavin-UVA CXL in AK

Regarding bacterial and fungal keratitis, many promising reports regarding Riboflavin-UVA CXL effect have been published. In a case series reported by Shetty *et al.*, CXL controlled non-resolving microbial keratitis treated previously with conventional antimicrobial agents (10). Six of nine bacterial and three of six fungal keratitis patients were fully resolved 4 to 6 weeks after CXL treatment. The time required for epithelial healing in these cases were 14 to 28 days. They also reported the resolution of pain on the first postoperative day of CXL due to the depletion of the corneal subepithelial nerve plexus. Of interest, sometimes, hypopyon increased after CXL and took longer periods of time for resolution than epithelial or stromal healing. Said *et al.* studied the effect of riboflavin-UVA CXL in advanced infectious keratitis (25). They divided 40 eyes of advanced infectious keratitis into two groups: medical treatment only *vs.* riboflavin-UVA CXL plus medical treatment. Although the time to corneal healing was not significantly shortened with CXL, the incidence of complications such as corneal perforation and recurrent infection was lowered with riboflavin-UVA CXL.

Although there are many reports on the efficacy of riboflavin-UVA CXL on bacterial keratitis, there have been only anecdotal reports about the effect of riboflavin-UVA CXL in the treatment of AK. In many reports, riboflavin-UVA CXL was used as adjuvant treatment in intractable AK treated with conventional topical biguanides. However, topical treatment is almost always continued after riboflavin-UVA CXL. Therefore it is difficult to isolate the effect of CXL. For clear demonstration of riboflavin-UVA CXL, comparison between groups with or without concomitant use of anti-acanthamoeba medication is necessary. Furthermore, bacterial superinfection is not uncommon in AK and should be suspected when the clinical response to anti-acanthamoeba treatment is limited or symptoms worsen (26).

The clinical effect of riboflavin-UVA CXL in AK was first reported by Ehlers *et al.* in 2009 (27). They applied riboflavin-UVA CXL in 3 eyes and 2 eyes completed the healing of corneal ulcers. Subsequently, Morėn *et al.* reported l case of successful treatment of AK by riboflavin-UVA CXL in 2010 (28). Although they did not confirm acanthamoeba infection either by culture or by histology, the clinical features of their case suggested AK. The clinical features worsened even with topical PHMB, and so they applied riboflavin-UVA CXL (5.4 J/cm^2). After the treatment, keratitis resolved slowly over 2 months. Shortly after Morėn *et al.*'s first case report, Khan *et al.* reported 3 cases of successful treatment of AK using CXL (13). After that, Chan *et al.* reported 1 case of successful treatment (29).

Price *et al.* applied 365 nm UVA light (3 mW/cm^2) for 15 to 45 minutes in 40 infectious keratitis patients (11).

Table 1 Summary of clinical reports of corneal collagen cross-linking (CXL) treatment for acanthamoeba keratitis (AK)

Year	Authors	Case number	Healed	Treatment protocol	Clinical outcomes	Complications	Note
2009	Ehlers *et al.* (27)	3	2	5.4 J/cm^2	2 eyes completed healing; 1 eye underwent enucleation	–	–
2010	Morèn *et al.* (28)	1	1	5.4 J/cm^2	Complete epithelialization in 32 days	–	Clinically suspected AK case
2011	Khan *et al.* (13)	3	3	5.4 J/cm^2	Complete epithelialization in 2 months	Two needed PK due to dense central corneal scar	repeated CXL at 1 or 2 weeks interval
2011	Garduño-Vieyra *et al.* (31)	1	1	5.4 J/cm^2	Clinical symptom improved 24h after CXL; disease was controlled at 3weeks after CXL	No	Culture positive AK
2012	Price *et al.* (11)	2	2	5.4 J/cm^2	Complete epithelialization in 54 in one eye and 145 days in the other eye	No	repeated CXL
2012	Panda *et al.* (32)	1	1	5.4 J/cm^2	Complete epithelialization in 8 days; complete resolution in 4 weeks	No	Culture positive AK
2012	Müller *et al.* (33)	1	1	5.4 J/cm^2	–	–	–
2013	Rosseta at al. (34)	1	1	5.4 J/cm^2	Complete epithelialization in 10 days	–	Culture positive AK
2013	Demirci *et al.* (35)	1	1	5.4 J/cm^2	Complete epithelialization in 10 days	No	Confocal microscopy
2014	Arance-Gil *et al.* (36)	1	1	5.4 J/cm^2	Anti-acanthamoeba medication stopped at 3 months after CXL; amniotic membrane transplantation for persistent epithelial defect at 6 months after CXL; penetrating keratoplasty at 8 months after CXL	Glaucoma and cataract	1 year of topical anti-acanthamoeba treatment with no improvement before CXL
2014	Said *et al.* (25)	1	1	5.4 J/cm^2	Complete epithelialization in 26 days	–	Faster epithelial healing compared to medication only control eyes
2014	Chan *et al.* (29)	1	1	5.4 J/cm^2	Significant symptomatic improvement and epithelial healing at 1 week	–	Confocal microscopy
2016	Hager *et al.* (30)	7	0	5 eyes: 32.4 J/cm^2; 2 eyes: 5.4 J/cm^2	Proceed to PK due to uncontrolled infection	–	Persistence of acanthamoeba cysts in 6 corneal buttons

The causative organisms were bacteria (24 eyes), fungal (7 eyes), acanthamoeba (2 eyes), virus (1 eye) and no identified organism (6 eyes). Six cases (2 bacterial, 3 fungal, and 1 without growth) failed to resolve even after riboflavin-UVA CXL and received penetrating keratoplasty. However, 2 cases of AK resolved after riboflavin-UVA CXL.

Hager *et al.* (30) raised a serious question about the amoebicidal effect of riboflavin-UVA CXL. They performed histological examination of corneal buttons obtained after penetrating keratoplasty due to intractable AK (30). These corneas had undergone riboflavin-UVA CXL (2 eyes with 5.4 J/cm^2 and 5 eyes with 32.4 J/cm^2) during the anti-acanthamoeba treatment before penetrating keratoplasty. The surprising finding was that acanthamoeba cysts and trophozoites persisted in the corneal tissue following riboflavin-UVA CXL in six out of seven corneal buttons.

Table 1 summarizes the case reports regarding riboflavin-UVA CXL in AK patients. It is noteworthy that most cases of AK eventually resolved with the treatment except Hager *et al.*'s cases.

Future investigation of riboflavin-UVA CXL in AK

It is noteworthy that there have been continuous anecdotal

reports of effective treatment of AK with riboflavin-UVA CXL. However, it is hard to find any *in vitro* and *in vivo* animal studies that clearly demonstrate amoebicidal or cysticidal effects of riboflavin-UVA CXL. Human eyes mount an active immune reaction to AK that is hard to reproduce in a laboratory environment or in animal models. Differences in the acanthamoeba burden in human disease and experimental setting can also contribute to this discrepancy.

Given the severity and intractability of AK, it is very important to establish an effective and systematic treatment protocol through the discovery of any possible treatments candidates and the demonstration of their effects. Therefore, it is necessary to conduct a prospective case-control study, ideally using three groups: topical anti-acanthamoeba medication only, riboflavin-UVA CXL only, and combined anti-acanthamoeba medication and riboflavin-UVA CXL.

Acknowledgments

Funding: The study is supported in part by a grant of Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2016R1D1A1B03931724).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Roy S. Chuck, Viral V. Juthani and Joann J. Kang) for the series "Refractive Surgery" published in *Annals of Eye Science*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aes.2019.01.06). The series "Refractive Surgery" was commissioned by the editorial office without any funding or sponsorship. RSC served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Illingworth CD, Cook SD. Acanthamoeba keratitis. Surv Ophthalmol 1998;42:493-508.
2. Dart JK, Saw VP, Kilvington S. Acanthamoeba keratitis: diagnosis and treatment update 2009. Am J Ophthalmol 2009;148:487-499.e2.
3. Claerhout I, Goegebuer A, Van Den Broecke C, et al. Delay in diagnosis and outcome of Acanthamoeba keratitis. Graefes Arch Clin Exp Ophthalmol 2004;242:648-53.
4. Lorenzo-Morales J, Khan NA, Walochnik J. An update on Acanthamoeba keratitis: diagnosis, pathogenesis and treatment. Parasite 2015;22:10.
5. Larkin DF, Kilvington S, Dart JK. Treatment of Acanthamoeba keratitis with polyhexamethylene biguanide. Ophthalmology 1992;99:185-91.
6. Siddiqui R, Aqeel Y, Khan NA. The Development of Drugs against Acanthamoeba Infections. Antimicrob Agents Chemother 2016;60:6441-50.
7. Subasinghe SK, Ogbuehi KC, Dias GJ. Current perspectives on corneal collagen crosslinking (CXL). Graefes Arch Clin Exp Ophthalmol 2018;256:1363-84.
8. Sorkin N, Varssano D. Corneal collagen crosslinking: a systematic review. Ophthalmologica 2014;232:10-27.
9. Papaioannou L, Miligkos M, Papathanassiou M. Corneal Collagen Cross-Linking for Infectious Keratitis: A Systematic Review and Meta-Analysis. Cornea 2016;35:62-71.
10. Shetty R, Nagaraja H, Jayadev C, et al. Collagen crosslinking in the management of advanced non-resolving microbial keratitis. Br J Ophthalmol 2014;98:1033-5.
11. Price MO, Tenkman LR, Schrier A, et al. Photoactivated riboflavin treatment of infectious keratitis using collagen cross-linking technology. J Refract Surg 2012;28:706-13.
12. 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;49:3402-8.

13. Khan YA, Kashiwabuchi RT, Martins SA, et al. Riboflavin and ultraviolet light a therapy as an adjuvant treatment for medically refractive Acanthamoeba keratitis: report of 3 cases. Ophthalmology 2011;118:324-31.
14. Hafezi F, Randleman JB. PACK-CXL: defining CXL for infectious keratitis. J Refract Surg 2014;30:438-9.
15. 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.
16. Wollensak G, Aurich H, Wirbelauer C, et al. Significance of the riboflavin film in corneal collagen crosslinking. J Cataract Refract Surg 2010;36:114-20.
17. Wollensak G, Sporl E, Reber F, et al. Corneal endothelial cytotoxicity of riboflavin/UVA treatment in vitro. Ophthalmic Res 2003;35:324-8.
18. Wollensak G, Spoerl E, Wilsch M, et al. Endothelial cell damage after riboflavin-ultraviolet-A treatment in the rabbit. J Cataract Refract Surg 2003;29:1786-90.
19. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003;135:620-7.
20. Kymionis GD, Kontadakis GA, Hashemi KK. Accelerated versus conventional corneal crosslinking for refractive instability: an update. Curr Opin Ophthalmol 2017;28:343-7.
21. del Buey MA, Cristobal JA, Casas P, et al. Evaluation of in vitro efficacy of combined riboflavin and ultraviolet a for Acanthamoeba isolates. Am J Ophthalmol 2012;153:399-404.
22. Kashiwabuchi RT, Carvalho FR, Khan YA, et al. Assessing efficacy of combined riboflavin and UV-A light (365 nm) treatment of Acanthamoeba trophozoites. Invest Ophthalmol Vis Sci 2011;52:9333-8.
23. Berra M, Galperin G, Boscaro G, et al. Treatment of Acanthamoeba keratitis by corneal cross-linking. Cornea 2013;32:174-8.
24. Atalay HT, Dogruman-Al F, Sarzhanov F, et al. Effect of Riboflavin/Rose Bengal-Mediated PACK-CXL on Acanthamoeba Trophozoites and Cysts in Vitro. Curr Eye Res 2018;43:1322-5.
25. 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;121:1377-82.
26. Bacon AS, Frazer DG, Dart JK, et al. A review of 72 consecutive cases of Acanthamoeba keratitis, 1984-1992. Eye 1993;7:719-25.
27. Ehlers N, Hjortdal J, Nielsen K, et al. Riboflavin-UVA treatment in the management of edema and nonhealing ulcers of the cornea. J Refract Surg 2009;25:S803-6.
28. Morén H, Malmsjo M, Mortensen J, et al. Riboflavin and ultraviolet a collagen crosslinking of the cornea for the treatment of keratitis. Cornea 2010;29:102-4.
29. Chan E, Snibson GR, Sullivan L. Treatment of infectious keratitis with riboflavin and ultraviolet-A irradiation. J Cataract Refract Surg 2014;40:1919-25.
30. Hager T, Hasenfus A, Stachon T, et al. Crosslinking and corneal cryotherapy in acanthamoeba keratitis -- a histological study. Graefes Arch Clin Exp Ophthalmol 2016;254:149-53.
31. Garduño-Vieyra L, Gonzalez-Sanchez CR, Hernandez-Da Mota SE. Ultraviolet-a light and riboflavin therapy for acanthamoeba keratitis: a case report. Case Rep Ophthalmol 2011;2:291-5.
32. Panda A, Krishna SN, Kumar S. Photo-activated riboflavin therapy of refractory corneal ulcers. Cornea 2012;31:1210-3.
33. Müller L, Thiel MA, Kipfer-Kauer AI, et al. Corneal cross-linking as supplementary treatment option in melting keratitis: a case series. Klin Monbl Augenheilkd 2012;229:411-5.
34. Rosetta P, Vinciguerra R, Romano MR, et al. Corneal collagen cross-linking window absorption. Cornea 2013;32:550-4.
35. Demirci G, Ozdamar A. A case of medication-resistant acanthamoeba keratitis treated by corneal crosslinking in Turkey. Case Rep Ophthalmol Med 2013;2013:608253.
36. Arance-Gil Á, Gutierrez-Ortega AR, Villa-Collar C, et al. Corneal cross-linking for Acanthamoeba keratitis in an orthokeratology patient after swimming in contaminated water. Cont Lens Anterior Eye 2014;37:224-7.

doi: 10.21037/aes.2019.01.06
Cite this article as: Park CY, Chuck RS. Riboflavin-UVA collagen cross-linking for the treatment of acanthamoeba keratitis. Ann Eye Sci 2019;4:7.

