ORIGINAL ARTICLE

Riboflavin/UVA photochemical therapy for severe infectious keratitis

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Purpose: *To describe the antibacterial activity of treatment with riboflavin and ultraviolet A light (UVA) in cases of severe infectious keratitis.*
Methods: *A retrospective analysis was performed of an interventional case series in which 6 eyes of 6 patients with severe infectious keratitis, all of whom were refractive to multidrug conventional therapy, were treated with riboflavin/UVA. The procedure was conducted according to the standardized protocol of corneal collagen crosslinking (CXL) for keratoconus. Best spectacle-corrected visual acuity and clinical outcomes were evaluated before and during the follow-up period.*
Results: *Five of the 6 patients showed rapid reduction in symptoms and decreased infiltrate size after riboflavin/UVA photochemical therapy. Signs of infection and inflammation mostly resolved within 1 to 2 weeks after the treatment. Despite this therapy, one patient continued to deteriorate, and penetrating keratoplasty was performed.*
Conclusions: *The adjunctive use of riboflavin/UVA photochemical therapy has a positive effect on refractory infectious keratitis. The treatment seems to be safe and effective and should be considered as part of the first-line therapy in severe cases of infectious keratitis.*

Keywords: *Collagen crosslinking, Cornea, Infiltrate, Riboflavin, Ultraviolet A light*

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INTRODUCTION

Photochemical corneal collagen crosslinking (CXL) using riboflavin and ultraviolet A light (UVA) for the treatment of progressive keratoconus has gained popularity in recent years, yielding promising data on long-term corneal stabilization and improvement of vision in these patients (1). A less familiar activity of riboflavin/UVA is its anti-infectious effect, although pathogen inactivation by riboflavin photosensitization using UV or visible light was first recognized in the 1960s (2). More recent reports indicate that microbes are damaged by nonspecific oxidative stress mediated by reactive oxygen species as well as by intercalation of the riboflavin molecule into the RNA and DNA of microorganisms (3-5). Inactivation of a wide range of microorganisms, including viruses, bacteria, and parasites, has been effectively achieved by this CXL technique (2, 6). For this reason, UVA photosensitization of riboflavin was recently suggested as a treatment against infectious keratitis (7), a proposal supported by several published case reports (8-11) and *in vitro* experiments (6, 7).
We describe 6 cases in which patients with severe corneal infiltration unresponsive to intensive topical medication underwent photochemical treatment with riboflavin/UVA as an adjunctive procedure.

TABLE I - PATIENTS' DEMOGRAPHIC DATA AND THE DESCRIPTIVE FEATURES OF THE KERATITIS ULCERS

KERATITIS ULCERS											
Patient	**Age, y**	**Systemic disease**	**Ocular history**	**Eye**	**BCVA at presentation**	**Ulcer size at presentation**	**Hypopyon**	**Antibiotics Before CXL**	**Microbial culture results**	**Follow-up, wk**	**BCVA at end of follow-up**
1	47	None	Soft contact lens use	LE	20/400	2 mm	0.2 mm	Vancomycin, ceftazidime, natamycin	*Pseudomonas aeruginosa, Staphylococcus epidermidis*	12	20/40
2	21	None	Soft colored contact lens use	RE	20/40	Multiple foci	No	Moxifloxacin, polyhexamethylene biguanide (PHMB), chlorhexidine, brolene	Negative	4	20/20
3	66	None	s/p PKP d/t corneal dystrophy	LE	20/100	3 mm	No	Cefamezine, garamycin, vancomycin, ceftazidime, fluconazole	Negative	3	20/60
4	42	None	s/p PKP d/t keratoconus	LE	20/100*	3 mm	No	Ceftazidime, cefamezine, garamycin, vancomycin	*Serratia marcescens, Mycobacterium chelonae*	8	20/25*
5	37	Crohn	Soft contact lens use	RE	20/40	2 mm	No	Ceftazidime, vancomycin, chlorhexidine brolene, amphotericin	Negative	8	20/30
6	65	Hypertension	s/p PKP d/t trachoma	LE	Hand Movement	5 mm	No	Ceftazidime, vancomycin	*Serratia marcescens*	2	NA

BCVA = best-corrected visual acuity; CXL = corneal collagen crosslinking; NA = not applicable; PKP = penetrating keratoplasty.
*After PKP.

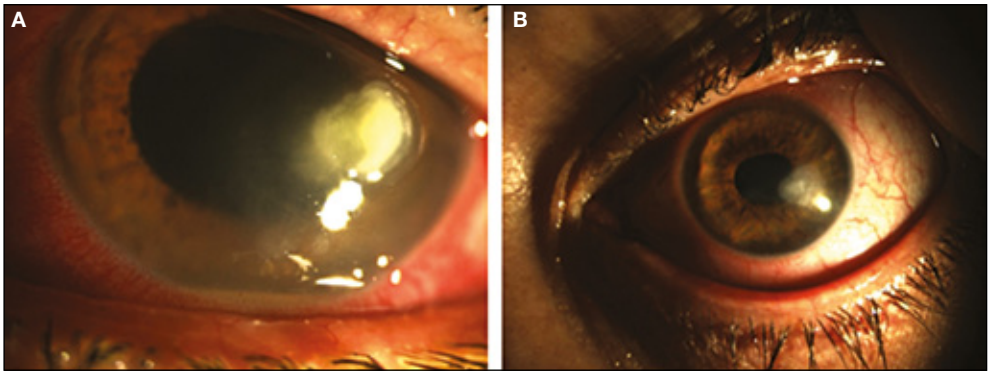

Fig. 1 - *A large corneal ulcer resulting from the use of soft contact lenses, accompanied by corneal edema and hypopyon (patient 1).* ***(A)*** *Before riboflavin/ultraviolet A light photochemical therapy and* ***(B)*** *3 months after treatment. All signs of inflammation had regressed within days of treatment, leaving only a corneal scar visible at the site of earlier infection. Epithelium had healed completely within 10 days.*

PATIENTS AND METHODS

Riboflavin/UVA photochemical therapy was performed in 6 patients with infectious keratitis refractive to medical treatment. All patients signed informed consent to participate in this retrospective analysis. The study was conducted according to the tenets of the Declaration of Helsinki and received approval from the Sheba Medical Center Institutional Review Board committee. Evaluation of best spectacle-corrected visual acuity (BSCVA) and slit-lamp biomicroscopy were performed preoperatively and during follow-up.
The procedure was conducted according to the standardized protocol of CXL for progressive keratoconus. After topical anesthesia, the fluffy corneal epithelium was carefully removed above the infiltrate and for 2 mm beyond its margins. Riboflavin drops (vitamin B2; Streuli, Uznach, Switzerland) 0.1% solution (10 mg riboflavin-5-phosphate in 10 mL dextran 20% solution) were administered every 5 minutes for 30 minutes, followed by UVA radiation for 30 minutes, while continuing with the same rate of application of riboflavin drops. The device used for UVA irradiation was the UV-X system (Peschke Meditrade GmbH, Huenenberg, Switzerland) at a wavelength of 370 nm and irradiance of 3 mW/cm^2, at a distance of 5 cm from the cornea. Upon termination of the procedure, antibiotic drops were instilled.

RESULTS

Between January 2010 and July 2011, 6 eyes of 6 consecutive patients were treated for severe infectious corneal keratitis or ulceration unresponsive to medical treatment. Table I summarizes patients' demographic data and the descriptive features of the keratitis ulcers.

Case 1

A 47-year-old healthy woman presented with a painful red eye and decreased vision of 3 days' duration LE. Prior to admission she had been treated for 3 days by her general physician with dexamethasone drops and chloramphenicol ointment, but without improvement. The patient had a history of myopia and wore daily disposable soft contact lenses. She mentioned that she had been wearing the contact lenses for several days without removing or replacing them, even while sleeping or showering. Upon admission, her BSCVA was 20/40 RE and 20/400 LE. Examination of the RE was unremarkable, whereas the LE had swollen eyelids, severe bulbar conjunctival infection, an annular paracentral ulcerated infiltrate, prominent anterior chamber flare, cells with precipitates on the endothelium, and a 0.2-mm hypopyon (Fig. 1A). Cultures for bacteria, fungi, and *Acanthamoeba* were taken from scrapings from the cornea, as well as from the contact lens containers and fluids. Topical treatment was initiated immediately thereafter with hourly vancomycin (50 mg/mL) and ceftazidime (50 mg/mL), as well as atropine twice a day. The cultures were positive only for *Pseudomonas aeruginosa*, which is sensitive to broad spectrum of antibiotics. Because of the lack of clinical improvement, however, after a therapeutic window additional scrapings for cultures were taken. These eventually grew *Staphylococcus epidermidis*. Topical antibiotic treatment was reinstituted and in view of the lack of improvement natamycin 5% was added.
Despite the intensive pharmacologic treatment, the clinical appearance suggested progression and worsening of the keratitis, with severe inflammation and fibrin formation in the anterior chamber. Therefore, on day 14 after her admission, the patient was given riboflavin/UVA photochemical

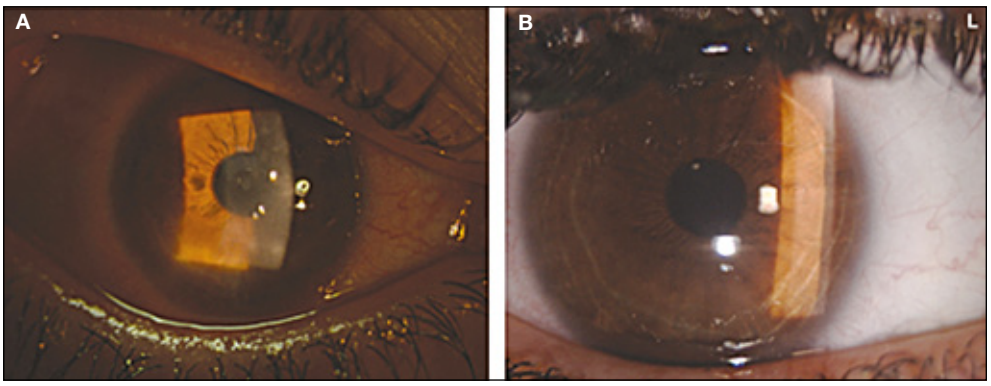

Fig. 2 - *Annular ring of semiopaque infiltrates in the superior and inferior corneal regions resulting from the use of soft contact lenses (patient 2).* ***(A)*** *Before riboflavin/ultraviolet A light photochemical therapy and* ***(B)*** *1 month after treatment.*

therapy. After the treatment, all medications were discontinued except for Vigamox (moxifloxacin 0.5%), which was reduced to 4 times daily. Within a few days, the pain and irritation had decreased, and gradual reepithelialization was evident (Fig. 1B). By 3 months after riboflavin/UVA treatment, visual acuity was 20/40, with minor stromal cicatricial tissue. There was no need for corneal transplantation or other surgical procedure.

Case 2

A healthy 21-year-old woman presented with worsening of pain, photophobia, and visual acuity following a few weeks of failure to respond to treatment with different kinds of topical antibiotics and steroids for a presumed bacterial keratitis in her RE. She reported using soft color contact lenses that were replaced monthly. On referral, her BSCVA was 20/40 RE and 20/20 LE. Severe bulbar conjunctival infection was evident. An annular ring of semiopaque infiltrates with a wall-like elevated border was visible in the superior and inferior parts of the cornea (Fig. 2A). Perineuritis was noted, and there was moderate anterior chamber flare. Examination of the LE was unremarkable.

Severe infectious keratitis was diagnosed, and cultures were grown from corneal scrapings, contact lens containers, and fluids. Topical treatment was started with hourly Vigamox (moxifloxacin 0.5%). In addition, because of a high clinical suspicion of *Acanthamoeba*, she was given topical polyhexamethylene biguanide (PHMB) every 3 hours and topical chlorhexidine 0.02% 4 times a day. Owing to the classic clinical appearance of *Acanthamoeba*, analysis for herpes simplex virus mRNA was not performed, even though some authors (12, 13) consider this to be a prerequisite for treatment with riboflavin/UVA because theoretically irradiation may activate herpes simplex. All laboratory tests were negative.

In spite of the pharmacologic treatment, over the following 2 weeks the keratitis progressed. On day 15, riboflavin/UVA photochemical therapy was performed. After the treatment, all medications were discontinued except for Vigamox (moxifloxacin 0.5%), which was reduced to 4 times daily. Within a few days after the procedure, the pain and irritation decreased, and no further necrotization was observed. Gradual reepithelialization began within a few days. Two weeks after the procedure, the ulcer was healed and the patient was free of pain, with only minimal corneal stromal cicatricial tissue remaining. By 1 month after riboflavin/UVA treatment, visual acuity was 20/20, the cicatricial tissue had faded, and the cornea was completely transparent (Fig. 2B). There was no need for corneal transplantation or other surgical procedure.

Case 3

A 66-year-old woman presented with a 1-week history of pain, photophobia, and foreign body sensation LE. Her ocular history included trichiasis, bilateral penetrating keratoplasty for treatment of corneal dystrophy 5 years previously, and pseudophakia. Examination at presentation revealed heavy ciliary and conjunctival infections. The patient's BSCVA was 20/25 RE and 20/100 LE. A large white corneal infiltrate was visible in the region of the central cornea, and was accompanied by mild corneal edema. Samples taken from the conjunctiva and cornea for culturing were all negative. Treatment was started with hourly topical cefazolin (50 mg/mL) and gentamicin (20 mg/mL), and as after 3 days there was no improve-

ment, these were replaced by hourly vancomycin (50 mg/mL) and ceftazidime (50 mg/mL). Because fungal keratitis was suspected, topical fluconazole 0.2% was added. Over the next few days, the keratitis progressed despite the pharmacologic treatment.

After 10 days, the patient received riboflavin/UVA photochemical therapy, and thereafter was instructed to apply ofloxacin 0.3% eyedrops 4 times a day. The corneal ulceration began to show signs of healing, with a decrease in cicatricial tissue and corneal edema. The patient reported significant improvement in symptoms and continued the ofloxacin 0.3% treatment for 3 more weeks. By 3 weeks after the procedure, the ulcer was completely healed and the patient had no pain. Some central stromal cicatricial tissue remained, however, resulting in a visual acuity of 20/60.

Case 4

A 42-year-old healthy man presented with a 4-day history of pain and photophobia LE. His ocular history included bilateral penetrating keratoplasty for treatment of keratoconus 5 years earlier. At presentation, BSCVA LE was 20/100. A white infiltrate, 3 mm in diameter, was visible in the central cornea. Corneal scrapings were sent for microbiological workup for bacteria, herpes simplex, and *Acanthamoeba*. Treatment was started with the broad-spectrum topical antibiotics cefazolin (50 mg/mL) and gentamicin (20 mg/mL) administered hourly, replaced 3 days later by hourly vancomycin (50 mg/mL) and ceftazidime (50 mg/mL). The cultures were positive for *Serratia marcescens*, which is sensitive to cefepime, ceftriaxone, ceftazidime, and amikacin.

Despite the targeted treatment the keratitis continued to progress, and riboflavin/UVA photochemical therapy was performed 10 days after initial presentation. A few days after the procedure, however, there was further deterioration accompanied by worsening of the BCVA to 20/200, and therapeutic penetrating keratoplasty was required. Postoperative treatment included dexamethasone 0.1%, cefazolin 50 mg/mL, and garamycin 14 mg/mL, each 4 times a day. The excised cornea was sent for laboratory examinations and *Mycobacterium chelonae* was detected. It is unclear whether this infection was secondary to the photochemical therapy, because the initial corneal cultures had not revealed this microorganism. Following the penetrating keratoplasty, the infection healed.

Case 5

A 37-year-old woman presented with a 1-week history of redness, pain, and photophobia RE. The patient had been using monthly disposable soft contact lenses. At presentation, BSCVA RE was 20/40. A 2-mm corneal infiltrate was visible in the inferior parts of the cornea accompanied by moderate anterior chamber flare and cells. Corneal scrapings were taken and empirical treatment was started with topical vancomycin (50 mg/mL) and ceftazidime (50 mg/mL) administered hourly. Because of lack of improvement, chlorhexidine 0.02% and amphotericin B (2 mg/mL) were added. Laboratory examinations for bacteria, herpes simplex, *Acanthamoeba*, and fungi were negative. No cysts or fungi were detectable on confocal microscopy. After 2 weeks of treatment with no improvement, riboflavin/UVA photochemical therapy was performed. After the procedure, all medications were discontinued except for Vigamox (moxifloxacin 0.5%), which was reduced to 4 times a day. Improvement was rapid, and the ulcer healed within a week, leaving a small stromal scar. By 8 weeks, minimal central stromal cicatricial tissue remained, resulting in a visual acuity of 20/30.

Case 6

A 65-year-old woman presented with a 6-day history of severe pain and irritation LE. Her ocular history included trachoma many years ago resulting in corneal opacity. She developed a retinal detachment 2 years prior to her admission and underwent a penetrating keratoplasty combined with pars plana vitrectomy and silicone oil injection. Her intraocular pressure was controlled with topical prostaglandin analogs and beta-blockers as well as oral carbonic anhydrase inhibitors. In addition, she was treated with topical steroids twice daily after an episode of graft rejection 6 months prior to her admission. At presentation, BCVA LE was hand movement. The conjunctiva was severely irritated, and a dense white infiltrate 5 mm in diameter was observed in the midperiphery of the graft along with an epithelial defect above it (Fig. 3A). Upon admission, corneal scrapings were obtained and sent for microbiological workup. Treatment was started with hourly fortified vancomycin (50 mg/mL) and ceftazidime (50 mg/mL). The cultures were positive for *S marcescens*, which is sensitive to cefepime, ceftriaxone, ceftazidime, and amikacin.

Despite the targeted treatment, the keratitis continued

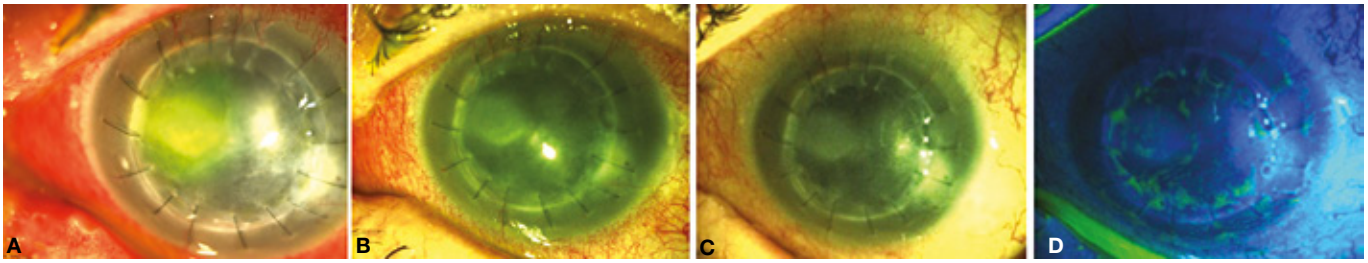

Fig. 3 - *A 5-mm corneal ulcer accompanied by corneal erosion and edema (patient 6).* ***(A)*** *Before riboflavin/ultraviolet A light photochemical therapy.* ***(B)*** *Four days after treatment and* ***(C)*** *6 days after treatment the corneal ulceration began to show signs of healing of the infiltrate and* ***(D)*** *closure of the epithelial defect (can be seen as absence of fluorescein staining). The patient reported rapid significant improvement in symptoms.*

to progress and the ocular pain worsened significantly. Riboflavin/UVA photochemical therapy was performed 11 days after initial presentation (5 days after her admission). Following the procedure, the antibiotic eyedrops were continued for another week 4 times daily. Within 2 days after the procedure, the corneal ulceration began to show signs of healing, with a closure of the epithelial defect and healing of the infiltrate (Fig. 3, B-D). At last follow-up, 2 weeks after the procedure, the patient reported rapid significant improvement in symptoms without a significant change in her known deteriorated visual acuity.

DISCUSSION

In this case series of 6 patients with severe infectious keratitis treated with riboflavin/UVA photochemical therapy, all but 1 patient (case 4) demonstrated rapid clinical improvement accompanied by major subjective relief.

The combination of riboflavin and UV light causes irreversible damage to the RNA and DNA of viruses, bacteria, and parasites, preventing them from replicating and causing disease (6, 8). Riboflavin alone does not appear to have any antibacterial effect (7) but its molecules form complexes with nucleic acids of pathogens, enabling UVA light to activate the complexes. This causes a chemical alteration in the functional groups of nucleic acids (primarily guanine bases), making pathogens unable to replicate. Ultraviolet A light, unlike UVB and UVC, does not damage DNA directly, but it can generate highly reactive chemical intermediates, such as hydroxyl and oxygen radicals, which in turn can damage DNA (9, 14).

Studies *in vitro* have demonstrated an antimicrobial effect of riboflavin/UVA photochemical therapy on a number of pathogens, including *P aeruginosa*, *Staphylococcus aureus*, *S epidermidis*, and others (7). Bacterial infectious keratitis pathogens (such as *P aeruginosa*) seem to be more sensitive to the photochemical therapy than amoeba or other species (15, 16). That finding was supported in our series by case 1, in which the patient produced cultures positive for *P aeruginosa* and a severe refractive corneal infiltrate that improved dramatically after the procedure.

Although secondary infections after CXL for keratoconus are rare, some case reports have been published. Garcia-Delpech et al (17) reported 3 cases of fusarium keratitis after CXL treatment. In our patient 4, in whom *M chelonae* was detected, the infection is probably an example of postprocedure infection because the cultures were negative prior to the procedure and, moreover, *M chelonae* is known to be one of the main ocular infections caused by nontuberculous mycobacteria (18). It has been reported after contact lens use (19, 20), penetrating keratoplasty (21), and refractive procedures including laser in situ keratomileusis and laser-assisted subepithelial keratectomy (22-28). It also has been associated with scleral buckle infections (29) and was rarely described after cataract extraction (30, 31).

In each of the 5 patients in whom the procedure was successful, only a brief period of minimal topical antibiotic treatment was needed after the procedure, and none had any intraoperative or postoperative complications. It seems likely that with additional experience and more precise definitions of the relevant criteria, physicians will find it possible to discontinue pharmacological treatment after photochemical therapy as soon as a positive response is observed.

Only sporadic publications have been published on the use of riboflavin/UVA photochemical therapy as an effective second-line treatment for severe refractory infectious keratitis (8-11). Our observations support these publications. Procedure-proven safety has been reported and damage to the corneal endothelium, the lens, or the retina is not ex-

pected when the standard protocol is used (32). Based on that report, and on the favorable clinical outcomes demonstrated in our patients, which were achieved within a short time of undergoing the procedure, we suggest that the use of UVA-riboflavin photochemical therapy should be considered as part of the first line of treatment in cases of severe nonresponding corneal infections. This approach, especially in the era of increasing microbial resistance to antibiotics, would reduce the use of topical antibiotics and their adverse effects, and would prevent the deterioration demonstrated here as a result of the failure of standard antibiotic treatment until the photochemical treatment was initiated. Makdoumi et al (33) recently reported promising results of a pilot study on riboflavin/UVA photochemical treatment as a primary therapy for bacterial keratitis. To obtain a reliable evaluation of the criteria, risks, and benefits of such an approach, a large-scale randomized clinical trial is warranted.

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