Riboflavin-UVA Treatment for Nonhealing Ulcers of the Cornea

To the Editor:

The case series study by Ehlers et al.,
which appeared in the September 2009 issue of the Journal of Refractive Surgery, presented the results of riboflavin-ultraviolet A (UVA) treatment in the management of edema and nonhealing ulcers of the cornea. Both the efficacy and safety of this method in the treatment of persisting nonhealing corneal ulcers were remarkable; 6 of 14 eyes with chronic nonhealing ulceration were healed after riboflavin-UVA application, while no complication occurred in any case subjected to the treatment mentioned above.

The antimicrobial efficacy of riboflavin/UVA for bacterial and fungal isolates was first documented in vitro by Martins et al.
in 2008. Ehlers et al., based on this evidence, tested the clinical efficacy of riboflavin-UVA irradiation in the treatment of nonhealing corneal ulcers and yielded most promising results.

Nevertheless, we would like to emphasize some critical points which, in our opinion, should be further clarified. The authors should elucidate whether riboflavin-UVA treatment was applied as a sole therapeutic method or if an adjuvant topical antimicrobial treatment was administered as well. If the latter is true, it would be extremely difficult for the clinician to evaluate the contribution of each therapeutic measure to the final outcome. It would also be of importance for the authors to report whether riboflavin-UVA treatment had an effect on the anterior chamber inflammation (cells, flare, hypopyon, etc), if any was observed.

We would also like to underscore the necessity for a proper evaluation of the corneal thickness and especially the depth of the corneal ulcer before any treatment with riboflavin-UVA irradiation. It is well established that during as well as after cross-linking induced by riboflavin-UVA in patients with keratoconus (thin corneas), corneal thickness is significantly reduced. The same effect on corneal thickness may be induced by the application of riboflavin-UVA in patients with corneal edema, as reported in the above mentioned study by Ehlers et al., Moreover, the recommendation for a minimum corneal thickness of 400 µm is considered to be essential to minimize the risk for potential endothelium impairment by direct UVA damage or by induced free radicals (photochemical damage). Would it not be reasonable to postulate that cross-linking in a patient with deep corneal ulcer may increase the risk for damage of corneal endothelium in this distinct area or even cause corneal perforation?

The authors do not provide data regarding the central corneal thickness or the depth and morphology (total size, vertical and horizontal diameter) of the corneal ulcers in the patients who were studied. Moreover, it is not clear whether the debris in the area of corneal ulcer was removed during the abrasion of corneal epithelium before riboflavin-UVA application. In 3 of 14 patients, a corneal grafting procedure/enucleation was required. Was the indication for corneal grafting in these cases an underlying pre-perforation condition or even corneal perforation? If not, why did the authors not use another therapeutic measure (amniotic membrane transplantation, autologous serum drops, etc) before proceeding with corneal grafting? If yes, would it not be possible that riboflavin-UVA treatment in distinct patients with extensive and deep corneal ulcers may have induced focal endothelial damage or even precipitated the development of corneal perforation?

We believe riboflavin-UVA irradiation in patients with corneal ulcers should be performed only after adequate morphological analysis of the ulcer area by anterior segment imaging (eg, anterior segment optical coherence tomography) and most important by precise evaluation of corneal thickness in the ulcer area. In patients with extensive deep corneal ulcers, other therapeutic options may represent more rational approaches, such as amniotic membrane transplantation, which is an effective and safe therapy of choice in persisting corneal epithelial defects, after the underlying infection has resolved.

Zisis Gatzionfas, MD
Berthold Seitz, MD
Homburg/Saar, Germany

REFERENCES


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Reply:

We thank Drs Gatzioufas and Seitz for their interest in our article on riboflavin-ultraviolet A cross-linking (CXL) management of nonhealing corneal ulcers.\(^1\)

The article briefly described 14 case reports of nonhealing corneal ulcers. In 6 cases, CXL resulted in a clear improvement of the clinical picture, with healing of the ulcers within 1 to 2 weeks. Concurrent ocular inflammation disappeared more or less completely within this period. In the remaining 8 cases, some healing was noted in 3 cases, whereas CXL treatment did not alter the clinical picture in 5 cases. All 14 patients had been treated by conventional medical therapy for their specific corneal disease before CXL, and continued this regimen after CXL treatment.

Gatzioufas and Seitz raise safety questions related to possible damage to the corneal endothelium in treating cases of nonhealing corneal ulcers with thinning of the corneal stroma. In most cases, the ulcers were superficial with underlying corneal edema resulting in a local corneal thickness >0.4 mm, but in some cases, smaller ulcers were present with stromal thinning to <0.4 mm. Overlying debris was removed before CXL. The size of these ulcers was <2 to 3 mm\(^2\). Cross-linking may have affected the corneal endothelium under these small ulcers, but the endothelium might have already been suffering in such areas. Small and localized endothelial damage may be a small price to pay if a chard corneal grafting can be avoided. Signs of endothelial damage were, however, not observed. Patients who underwent enucleation or regrafting had uncontrollable active infection despite massive antimicrobial therapy. We do not find amniotic membrane grafting attractive in cases of active infectious keratitis.

As mentioned in our conclusion, we agree that it remains to be elucidated to what extent and by which mechanisms CXL treatment of corneal ulcers may be beneficial. Anterior segment optical coherence tomography could be useful in the planning and follow-up of such patients, but we do not find it mandatory. A thorough and proper semi-quantitative slit-lamp evaluation may suffice.

Jesper Hjortdal, MD, PhD
Aarhus, Denmark

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