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Letter to the Editor

Novel matrix ReGeneraTing Agent promotes rapid corneal wound healing

Corneal neurotrophic ulcers are among the most difficult ophthalmological conditions to treat. Elimination of toxic agents and use of preservative-free lubricants are often first-line treatments, but these currently available topical therapies may be insufficient in promoting the healing response. Other measures include the use of autologous serum, conjunctival flaps, tarsorrhaphy and amniotic membrane grafting.[1] However, surgical techniques entail other risks, including central corneal scarring.

A new matrix therapy agent (ReGeneraTing Agent [RGTA]; Cacicol20) has recently been introduced that provides a matrix to promote cell migration. This matrix also has a novel property of binding growth factors that additionally offer cues for migrating cells.

We wish to report our successful initial experience with RGTA. Our patient inadvertently used more frequent dosing in the first week, and it is our observation that this resulted in a rapid healing response.

An 81-year-old woman with a history of bilateral pseudophakia, chronic blepharitis, limbal stem cell deficiency and long-standing bilateral corneal and conjunctival scarring secondary to trachoma was referred with a large epithelial defect in her left eye. On examination her visual acuity was 1/60 bilaterally. The left cornea was anaesthetic with intact conjunctival sensation. Despite standard management of the ocular surface disease, including topical antibiotics, topical steroids, topical lubricants, systemic tetracyclines, systemic azithromycin, in addition to the use of preservative-free medications, the large epithelial defect remained resistant to healing. The patient declined to have surgical intervention. In total, the neurotrophic defect was present for eight weeks. At her fifth clinic review, the topical neurotrophic growth factor, RGTA, was introduced.

The patient inadvertently used RGTA four times a day during the first week, along with preservative-free chloramphenicol (bd) and Lacrilube (Allergan, Irvine, CA, USA) nocte. After one week of RGTA treatment, there was a significant reduction in the epithelial defect from measuring 9 mm × 7 mm (at largest horizontal and vertical dimensions) to 3 mm × 2.4 mm. Healing continued with complete closure of the defect by week three of RGTA treatment (Fig. 1).

The cellular and molecular events involved in the healing response are complex. The early phases of healing are characterized by deposition of extra cellular matrix (ECM), and proliferation and migration of cells within this matrix, which act as a scaffold. Irrespective of the underlying cause, inflammation typically results in tissue destruction leading to ulceration and scarring. Pathological activity of proteolytic enzymes and active pro-inflammatory cytokines are implicated in the progression of tissue destruction.

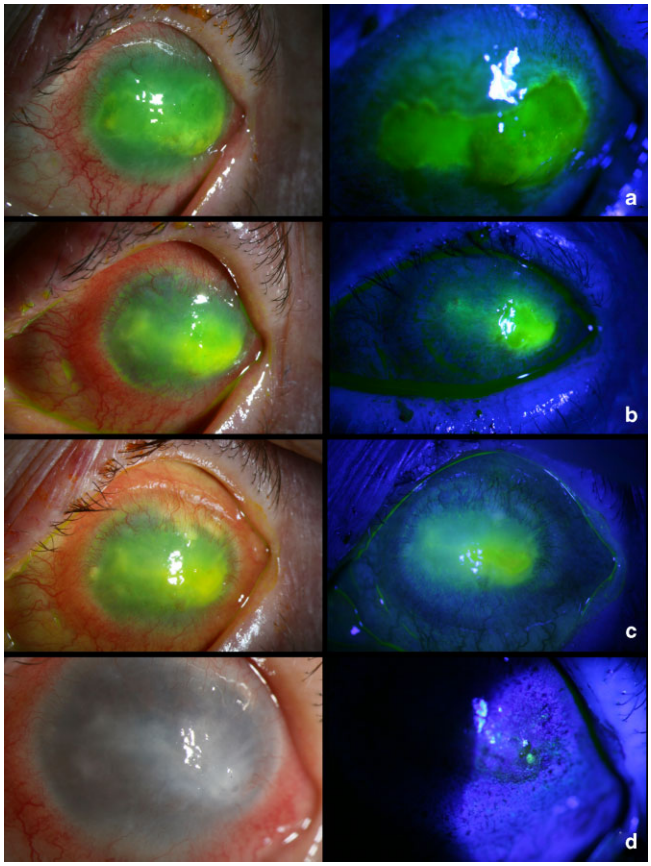

Figure 1. Image showing initial neurotrophic epithelial defect and the weekly stages of healing following treatment with ReGeneraTing Agent (RGTA).

Heparan is a key ECM component, holding collagen fibrils together and providing binding sites for growth factors. Injury to tissues results in loss of heparan in the ECM and the bound growth factors. Polymers that mimic the binding action of heparan may offer a matrix for growth factors to bind and cue cell migration and proliferation. Tissue regenerating agents (RGTA) are designed to encourage healing by mimicking the action of destroyed heparan-sulphate molecules, thereby recreating a cellular environment in which cells can multiply and migrate.

Application of RGTA has been demonstrated to accelerate the healing of skin ulcers.[2] Clinical application of RGTA on corneal ulcers has also shown promising results, including in those ulcers resulting from post-infectious keratitis, chemical burns and neurotropic ulcers.[3]

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Acute injury and the tissue remodeling both release lytic enzymes known as matrix metalloproteinases that degrade the ECM, initiating a negative repair–destruction cycle.[4] RGTA may halt the progression of this breakdown cycle, improve collagen reorganization and have an anti-fibrotic action properties which are favourable in corneal wound healing.

RGTA (Cacicol20) is supplied as a sterile single-dose solution of alpha 1–6 polycarboxymethyl glucose sulphate and penetrates into the cornea without crossing Descemet's membrane. The frequency of application of this agent is yet to be determined. When all heparan-binding sites available in wound tissue are occupied by RGTA, excessive application may compete with heparan-binding growth factors. Heparan-bound growth factors/cytokines stored in the RGTA matrix could then be competitively removed, reducing healing efficacy. Based on this concept, the regimen of one drop every second day has been advocated, with daily or more frequently dosing of RGTA deemed to be inefficient.[5]

In our case, successful closure of the neurotrophic epithelial defect was observed within three weeks of RGTA treatment. The rapid healing response following inadvertent instillation of RGTA four times a day suggested that there may be additional mechanisms of action. Factors that propagate the negative repair–destruction loops are pro-inflammatory cytokines and free radicals. It is possible that excessive application of RGTA may remove these damaging cytokines from the ocular environment, thereby breaking the negative repair/destruction cycle, similar to a loading dose principle. While our case report provides further clinical evidence to suggest that RGTA may promote rapid healing, further in vitro studies and clinical trials are required to realise the full potentials of this novel agent.

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