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Matrix regeneration therapy: a solution to enhance healing in fungal keratitis

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PEER REVIEW

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Comments

This is a good case report in which the authors managed to treat two cases of non-healing epithelial defect as a result of chronic presumed fungal keratitis which healed successfully with matrix therapy.
Details on Page 52

ABSTRACT

Corneal ulcers, especially of fungal origin, are a relatively common clinical entity within the spectrum of keratitis in tropical countries. The persistence of a non-healing epithelial defect is a known complication of these ulcers. Despite advances in medical therapy, the management of this condition is still challenging. CACICOL20® is a new ophthalmic matrix therapy that has been proved efficient as a corneal healing agent. To the best of our knowledge there have been reports of the limited use of matrix therapy in ocular healing, specifically in fungal keratitis. We report 2 cases of the efficacy of it as an adjuvant to topical amphotericin B in treating non-healing epithelial defects secondary to fungal corneal ulcers.

KEYWORDS

Fungal ulcer, Non healing epithelial defect, Matrix regeneration therapy

1. Introduction

A new matrix therapy, based on ReGeneraTing agents (RGTAs) as a wound healing agent, is currently being explored by clinicians. RGTAs are biodegradable polymers which are engineered to mimic and replace the glycosaminoglycan heparin-sulfate in the extra-cellular matrix of damaged tissue[1].

This matrix therapy based on RGTA technology has been documented by robust preclinical studies, and today specific RGTA molecules have been adapted to clinics for topical use in skin and corneal ulcers[1-5]. CACICOL20® is an ophthalmic medical device based on the RGTA molecule OTR4120 which is used to restore the corneal extracellular matrix microenvironment and has aroused great interest among clinicians[5]. However, there is still limited knowledge on its effect on humans.

We present 2 cases of non-healing epithelial defect as a result of chronic presumed fungal keratitis which healed remarkably and successfully with matrix therapy (CACICOL20®).

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2. Case report

2.1. Case 1

A 34-year-old man presented with sudden onset of pain and redness of the left eye for 6 d. It was associated with eye discharge. There was no history of ocular vegetative trauma or history of foreign body. He was initially treated on over-the-counter eyedrops. However, the condition worsened. He noticed a corneal opacity developing in his left eye 2 d prior to the presentation. On examination, visual acuity in the left eye was 6/24 with pinhole of 6/18 while the right eye was 6/6. The left eyelids were swollen and the conjunctiva was injected. There was presence of corneal ulcer inferonasally measuring 4.5 mm×4.0 mm, involving the deep stromal layer, with a feathery infiltrate at the margin. The surrounding cornea was oedematous. There was no hypopyon (Figure 1A). The fundus in the right eye was not visualised. The anterior segment and fundus of the fellow eye was unremarkable. Corneal scraping for Gram staining revealed no organism while culture and sensitivity later showed no growth of organism.

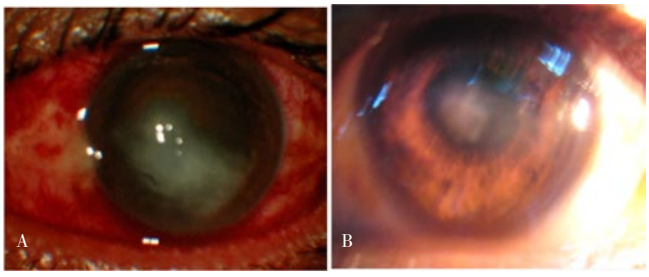

Figure 1. Left eye of the patient before treatment and after treatment.
A: Pre-treatment, B: After CACICOL20® treatment.

He was clinically diagnosed as presumed fungal keratitis. Initial antifungal therapy was started with intensive topical amphotericin B 0.15%, loading dose followed with hourly dosing. However, he responded poorly despite of a week of intensive topical treatment. Subsequently, amphotericin B (0.0005%) was injected intrastromally followed by a second injection a week later.

There was a marked improvement in terms of depth of ulcer and the stromal infiltrates after the intrastromal injection. The ulcer was completely healed a week later after a second injection of intrastromal amphotericin B. However, the remaining epithelial defect measuring 2.6 mm×2.4 mm exhibited slow healing. Two months later, there was still a persistent non-healing epithelial defect measuring 1 mm×1.8 mm. He also had persistent pain. A total of three doses (0.33 mL per dose) of matrix regeneration therapy (CACICOL20®) were instilled as a single drop application each time, with an interval of one week between doses. There was remarkable improvement with the above treatment. The epithelial defect healed completely after six weeks of treatment, leaving a faint scar (Figure 1B). There was a significant decrease in pain. The visual acuity of the left eye improved to 6/12 with pinhole of 6/9.

2.2. Case 2

A 59-year-old farmer with diabetes mellitus presented with sudden onset of pain and redness of the left eye for 5 d duration. It was associated with blurring of vision, mucoid eye discharge and epiphora. He had a history of vegetative trauma in the left eye two days prior to the symptoms.

On examination, visual acuity in the left eye was counting finger at 1 meter, while the right eye was 6/12. The conjunctiva was injected, with presence of mucoid discharge. The corneal sensation was reduced in the left eye. There was a central epithelial defect measuring 2.8 mm ×4.8 mm. It was surrounded by a ring of stromal abscess from 12 to 9 o'clock. Small satellite lesions were present at end of the ring of stromal abscess. There was no hypopyon (Figure 2A). The intraocular pressure was normal. The fundal view of the left eye was hazy. The anterior segment examination of the fellow eye revealed immature cataract. There was no diabetic retinopathy in the fundus. Cornea scraping for Gram staining revealed no organism while culture and sensitivity later showed no growth of organism. He was diagnosed clinically as presumed fungal keratitis with superimposed bacterial infection. He was put on intensive topical amphotericin B 0.15% (one drop every hour) and topical fortified gentamicin 1.5%.

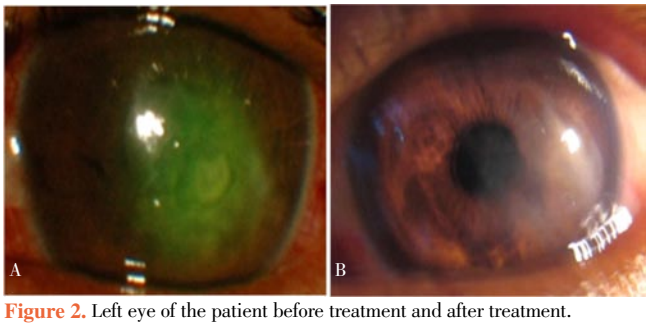

Figure 2. Left eye of the patient before treatment and after treatment.
A: Pre-treatment, B: After CACICOL20® treatment.

The stromal abscess resolved with treatment leaving Descemet folds and epithelial oedema. However, there was slow healing of the epithelial defect, which measured 1.6 mm×1.4mm prior to matrix generation therapy. Subsequently, he was started on two doses (0.33 mL per dose) of matrix regeneration therapy (CACICOL20®), which were instilled as a single dose a week apart. Two months after the matrix therapy, the epithelial defect was completely healed (Figure 2B) leaving a thin central corneal

scarring. The left visual acuity had improved from counting fingers to 6/60 with pinhole of 6/24.

3. Discussion

Glycosaminoglycan heparin-sulfate plays a central role in the organisation of the extra-cellular matrix scaffold by bridging matrix proteins, as well as fixing and protecting cytokines and growth factors within the cells microenvironment. When injured, heparin-sulfate are rapidly destroyed by glycanases and do not protect local growth factors from degradation by proteases. Signals brought by inflammatory and circulating cells trigger the repair process, but lead to a fibrotic response and loss of tissue quality. Furthermore, this destruction repair process may become recurrent, as in chronic wounds[1-5].

RGTAs is a non-degradable heparin-sulfate and resistant to mammal glycanases[2]. It contains biopolymers which are produced by controlled chemical substitution of dextran polymers at selected positions of carboxymethyl and sulfate groups[1,6]. RGTA will facilitate bridge matrix proteins in a scaffold organisation and protect from proteolysis by steric inherence. Introducing RGTA in a disorganised matrix will not only provide a new extra-cellular matrix scaffold, but also the spatial organization needed for communication peptides newly synthetised by neighbouring cells to home in the extracellular matrix microenvironment[3]. Hence it has the capability to serve as a healing agent[1-5].

RGTA was found to enhance wound healing in skin burns and bone in animal models[1,4]. Tong *et al.*[3] demonstrated treatment with an RGTA known as OTR4120 which improved healing in pressure ulcers induced in a rat model by reducing inflammation, stimulating angiogenesis, increasing collagen bio-synthesis and enhancing biomechanical strength. The study done by Groah *et al*. demonstrated that RGTA was safe and promoted wound healing in patients with chronic wounds from diabetic, pressure and vascular ulcers[7]. Similar results were reported in 2011 by Desgranges *et al.*[8] in treating patients with critical ischemia and there being no possibility of vascular surgery. A pilot study done by Chebi *et al*. suggested that RGTA OTR4120 favored corneal wound healing in treatment-resistant corneal ulcers and corneal dystrophy[9]. Aifa *et al.* also suggested RGTA as an alternative in treating the cornea surface following neurotrophic keratopathy[10].

In both patients presented above, there was a slow-healing epithelial defect secondary to chronic fungal ulcer. It is well known that the natural history of fungal keratitis results in a very slow-healing course and is difficult to treat. A persistent epithelial defect is usually difficult to treat and unresponsive to the conventional treatments such as unpreserved artificial tears, soft contact lens bandage or patching. Various alternative treatments, such as topical nerve growth factor[11], topical tymosin beta 4[12], autologous serum[13], and amniotic membrane transplantation[14] were studied and showed promising results. Nevertheless, our results support the use of RGTA in corneal surface healing defects and unresolved pain as a more innovative and effective solution.

We used CACICOL20®, an ophthalmic medical device based on RGTA, to treat our patients. This resulted in significant improvement of the keratitis and reduction of pain scores[5]. The safety and efficacy in treating patients with severe keratitis or painful corneal ulcers has been reported in previous studies[9].

Both our patients had complete healing of the epithelial defect with minimal corneal scarring after three and two doses of CACICOL20® respectively. Our first patient had a significant reduction of pain and improvement in visual acuity. The antioxidative and antifibroblast proliferation effects of RGTA may have contributed to this observation. The pain reduction was attributed to the improvement of extracellular matrix surrounding the corneal sensory nerve endings[9]. In the second patient, the management of the patient was more challenging because the patient had underlying diabetes mellitus with reduced corneal sensation. The pre-existing ocular neurotrophic condition altered the metabolism and integrity of the corneal epithelium and impaired epithelial wound healing[11]. However, matrix regeneration therapy with CACICOL20® was effective in promoting healing in this patient. Low treatment frequency (two to three doses of a single instillation weekly) was well tolerated by both patients. These case reports show that matrix regeneration therapy enhances healing of slow-healing epithelial defects in presumed fungal keratitis. Additionally, no reaction or complication was reported by these patients.

In conclusion, RGTA is a promising treatment in promoting healing in epithelial healing in fungal keratitis. It is well tolerated. Matrix regeneration is a recommended therapy in poorly-healing fungal keratitis.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

Matrix regeneration therapy is a new ophthalmic matrix therapy which is used to restore the corneal extracellular matrix microenvironment and has aroused great interest among clinicians.

Research frontiers

This case report shows that matrix regeneration therapy enhances healing of slow-healing epithelial defects in presumed fungal keratitis and also has the advantage to reduce the pain in painful corneal ulcer.

Related reports

The safety and efficacy in treating patients with severe keratitis or painful corneal ulcers has been reported in previous studies[9].

Besides treating poor epithelial healing and painful corneal ulcer, the other study also has demonstrated that RGTA was safe and promoted wound healing in patients with chronic wounds from diabetic pressure and vascular ulcers[7].

Applications

This case report suggests that matrix regeneration therapy is a promising treatment in promoting healing in epithelial healing in fungal keratitis.

This matrix regeneration therapy is not only can be used in cases of poor healing in fungal keratitis, but it can also be used in other causes of poor corneal epithelial healing.

Peer review

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