Topical Application of a Regenerative Agent for the Treatment of Persistent Epithelial Defects After Penetrating Keratoplasty

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ABSTRACT

Purpose: The aim of this study was to report two cases of persistent epithelial defects (PEDs) after penetrating keratoplasty successfully treated with topical application of a regenerative agent (RGTA; Cacicol[20])

Methods: This is a case series.

Results: Two patients suffering from a PED and unresponsive to conventional therapy were treated with application of Cacicol[20]. The PED healed in all patients and no side effects were noted.

Conclusions: Our cases show revealed that topical application of Cacicol[20] may be used with success for the treatment of PED after PKP.

Keywords: Persistent epithelial defects; penetrating keratoplasty; Cacicol

INTRODUCTION

Persistent epithelial defect (PED) is defined as full-thickness loss of epithelial cells that do not show healing for more than 2 weeks despite conventional treatment.[1,2]

PED may result from both ocular and systemic disorders, such as dry eye, chemical injury, microbial infection, neurotrophic keratitis, Stevens–Johnson syndrome, diabetes mellitus and ocular cicatricial pemphigoid. PEDs could lead to stromal degradation and thinning and in advanced cases, the cornea may perforate. PEDs occurs in 3.4% of eyes after penetrating keratoplasty (PKP)[3] and it may lead to vision-threatening complications because of infection, ulceration, neovascularization and scarring and may hamper PKP survival.[4,5]

Several approaches have been proposed for the treatment of PEDs such as artificial tears, eye patching, punctal plugs, contact lens, autologous serum eye drops, amniotic membrane graft and tarsorrhaphy.[6-10]

Regenerating agents (RGTAs) are a new pharmaceutical family that promotes tissue regeneration. By replacing and mimicking the action of destroyed glycosaminoglycan heparan sulfate, RGTAs act as a scaffold to promote fixation and proteolytic protection for the extracellular matrix microenvironment and components involved in tissue healing.[11]

Cacicol[20] belongs to the RGTA family that binds to matrix proteins and protects them from proteolysis; this permits the extracellular matrix microenvironment to restore its original architecture. This new agent has been reported to be an alternative or additional therapeutic regimen when treating corneal neurotrophic ulcers and compromised corneas.[11–14]

Here in, we present two patients with PEDs who were successfully treated with an RGTA (Cacicol[20])

CASE REPORTS

CASE 1

A 79-year-old woman was monitored in our department due to a bullous keratopathy in her left eye, which was caused by a complicated cataract surgery with posterior capsule tear, vitreous loss and need of anterior vitrectomy. Her best corrected visual acuity (BCVA) was hand movements. She had undergone a PKP and after two weeks the slit-lamp examination showed an extended graft epithelial defect (Figure 1A and 1B). The PED was resistant to conventional treatment for four weeks. Conventional therapy included pressure patch, topical antibiotic and steroid eye drops (ofloxacin and fluorometholone) and monodose artificial tears.

Due to treatment failure topical application of an RGTA (Cacicol[20]) was prescribed (instillation of 1 drop in alternate days) with reduction of the previous treatment.

One week later (Figure 2A) the defect was reduced to half and four (Figure 2B) weeks after Cacicol[20] commenced the slit-lamp examination showed complete corneal epithelial healing. There was no event of recurrence during the 6-month follow-up.

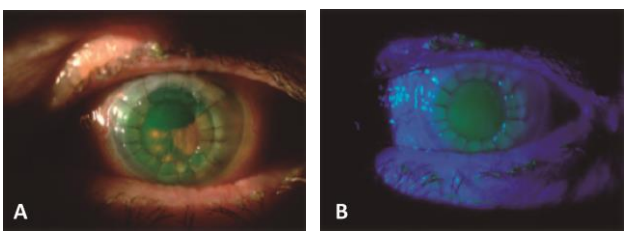

Figure 1 - Slit-lamp images of the left eye (case 1) two weeks after PKP

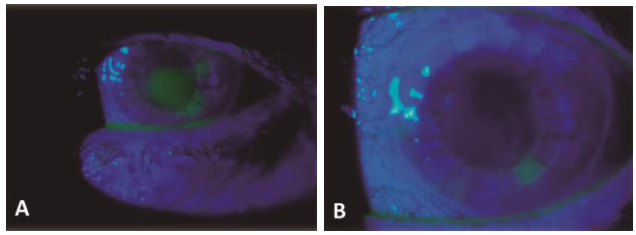

Figure 2 - Slit-lamp images of the left eye (case 1) one week (A) and four weeks (B) after treatment with Cacicol[20]

CASE 2

A 68-year-old man was referred to our department for the management of a corneal leukoma in his left eye. He had undergone lower eyelid surgery in the left eye for trichiasis correction six years ago with resolution of the lid abnormality. Five years ago he had undergone complicated cataract surgery with posterior capsule tear and vitreous loss. Anterior vitrectomy was performed and a posterior chamber intraocular lens was inserted in the ciliary sulcus. On ophthalmology examination, the patient had BCVA of 0,05 (Snellen scale) in left eye. He had undergone a PKP without complications on postoperative day one (Figure 3A). After one week the examination showed an extended graft epithelial defect (Figure 3B). At this moment corticoid drops was reduced, artificial tears was raised and pressure patch was prescribe. Two weeks after this treatment there was no changes in epithelial defect.

The PED was resistant to conventional treatment for six weeks. Conventional therapy during this period included the use of contact lens, pressure patch, artificial tears and two amniotic membrane grafts (Figure 4A). One week after Cacicol[20] application (instillation of 1 drop in alternate days) the dimensions of the epithelial defect decreased and five weeks later (six weeks after the treatment commenced), slit-lamp examination showed complete corneal epithelial healing (Figure 4B). During the 6-month follow-up, no recurrence was observed.

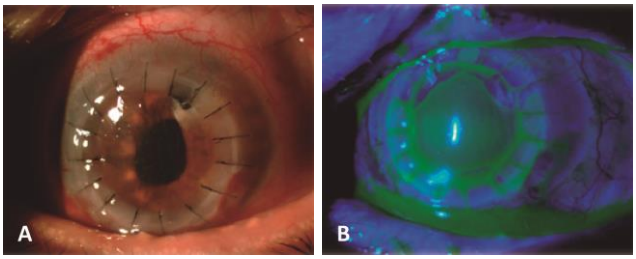

Figure 3 - Slit-lamp images of the left eye (case 2) one day (A) and one week (B) after PKP

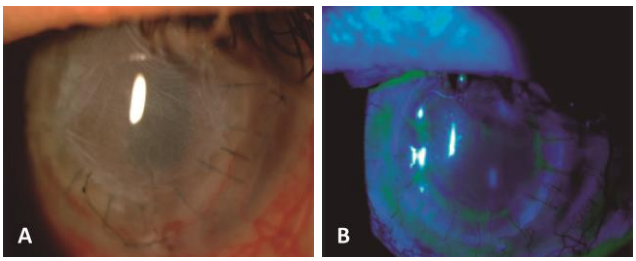

Figure 4 - Slit-lamp images of the left eye (case 2) with amniotic membrane graft and contact lens (A) and six weeks (B) after treatment with Cacicol[20]

DISCUSSION

Managing the PED after PKP should be as fast as possible due to possible severe consequences which may occur. Besides that it can be both an arduous task for the ophthalmologist and a burden to the patient. Several approaches have been proposed for the treatment of PEDs such as artificial tears, eye patching, tarsorrhaphy, autologous serum eye drops, amniotic membrane graft and topical application of autologous limbal stem cells.[6-10] However, in some cases, these treatments (combined or not) tend to be ineffective thereby prolonging patient discomfort and their diminished visual acuity, as well as requiring frequent clinic follow-up at a cost to society and worker productivity.

RGTA comprise a family of biodegradable glucose based polymers and it seems to be a promising therapeutic agent for controlling ocular surface inflammation and promoting corneal healing. By creating a cellular microenvironment that favors healing, Cacicol[20] has been shown to enhance the speed and quality of tissue healing.[11]

Cacicol[20] has already been used as a monotherapy for the treatment of ocular surface disorders such as neurotrophic ulcers and keratitis.[13,14] Aifa et al[13] reported corneal healing in 8 of 11 patients treated with an RGTA (Cacicol[20]) as monotherapy at a dosage of a single drop every 2 days, with 1 case of recurrence.

Still in this behavior, in 2015, I. Alcalde et al[15] reported the effectiveness of Cacicol[20] in an experimental model of corneal ulcer after photorefractive keratectomy (PRK) in mice. They concluded that corneas treated topically with Cacicol[20] for 7 days showed a greater degree of transparency when compared to controls and improved their epithelial cytoarchitecture. They also analyse myofibroblast transformation profiles in the stroma and concluded that Cacicol[20] reduced or delayed the presence of myofibroblasts in the stroma compared to balanced salt solution. In this way, the authors propose that the treatment with RGTA may have an additional useful action in the clinic after the PRK surgery since RGTA avoiding myofibroblast scarring formation and promoting nerve regeneration.

On the other hand, in 2016, Riku P. J. Arvola et al[11] presented an uncontrolled prospective case series of 6 patients with severe corneal neurotrophic ulcers treated with topical RGTA at a dose of 1 drop every second day. However their results were not as promising as they would like, since treatment was considered failure in 4 patients and 1 patient had corneal perforation. In this way they concluded that RGTAs probably have limited benefits in patients with severe corneal neurotrophic ulcers. As in our cases, none of their patients showed improvement in BCVA after treatment.

In this article we report our experience in two patients who presented with a PED resistant for conventional treatment. This patients after topical instillation of Cacicol[20] improved their clinical condition with complete corneal healing. There were no RGTA-related local or systemic side effects. Nevertheless we cannot forget some limitations of the work: first, the small number of cases to be evaluated; second, none of our patients were treated with autologous serum, so we don't know if there would be resolution of PED with this conventional treatment; and third, in both patients, RGTA was used in addition to a set of other pharmacological agents, that constitutes a bias for the estimation of the efficacy of RGTA.

CONCLUSION

In conclusion, our cases show revealed that topical application of Cacicol[20] seems to be an effective and safe alternative therapeutic approach for the treatment of PEDs after PKP. Nevertheless, further studies with a larger number of patients are needed to evaluate treatment potential.

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