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New Regenerating Agents (RGTA): New Indications in Persistent Corneal Thinning Caused By Fungal Keratitis

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Abstract

Purpose: To assess the effectiveness of new RGTA like Cacicol20 in two cases of persistent corneal ulceration refractory to maximum medical treatment in the context of fungal keratitis.

Methods: Case 1 was a 75-year-old woman with malocclusion after ptosis surgery who presented *Candida albicans keratitis* (yeast). Case 2 was a contact lens wearer 39-year-old man who presented *Fusarium keratitis* (filamentous fungus). They both improved with antifungals. However, the corneal thinning caused by the infection persisted despite artificial tears, autologous serum and a bandage contact lense (BCL). OCT showed 226 microns corneal thickness in Case 1 and descemetocele in Case 2. Cacicol 20 one drop every two days for one month was prescribed to both of them at that moment, when the infiltrates still persisted.

Results: After that regimen, Case 1 corneal thickness rose to 391 microns, and Case 2 rose to 224 microns. Complete epithelial healing was achieved in both cases. The infiltrates continued to decrease and they were eventually replaced by sterile leukomas. None of the patients presented new signs of infection afterwards. No precipitates appeared on the BCLs. None of the patients reported any adverse effects.

Conclusion: New RGTA like Cacicol20 could be an effective option for persistent corneal ulceration refractory to maximum conventional medical treatment, which would save surgical procedures. Moreover, they could be prescribed during fungal infection, despite the contraindication in case of active ocular infection that appears in the leaflet of Cacicol20.

Keywords: New regenerating agents (RGTA); Cacicol20; Fungal keratitis; Persistent corneal ulceration; Persistent epithelial defect

Introduction

Persistent corneal ulceration can occur as a consequence of three types of causes: exposure, neurotrophic disorders and total limbal stem cell deficiency. Exposure can be due to palpebral disorders such as entropion or after ptosis surgery (Table 1). Neurotrophic disorders can be caused by corneal infection among many others (Table 2), and they produce impaired corneal sensitivity, which hampers the process of healing [1].

There are several medical treatments that can be combined for the initial management of persistent corneal ulceration such as tear substitutes, autologous serum, growth factors, bandage contact lenses, moist chamber goggles or punctal occlusion. If these options fail, we can resort to surgical treatments such as tarsorraphy, amniotic membrane transplantation or keratoplasty [2].

The new regenerating agents (RGTA) like Cacicol® (Théa Laboratoires, 12 Rue Louis-Blériot 63 000 Clermont-Ferrand FRANCE) have emerged recently. These agents are biopolymers that mimic heparin sulfates [3]. They reduce the expression of urokinase-type plasminogen activator, metalloproteinase 9, nitric oxide synthase and xanthine oxidase, which helps to restore the matrix protein and cytokine balance and reduces proteolytic, oxidative and nitrosative damage. Consequently inflammation and neovascularization decrease, which enhances corneal regeneration [4].

VII cranial nerve palsy
Palpebral disorders: ectropion, scarring (trauma, chemical burn, herpes zoster ophthalmicus), ptosis surgery, blepharoplasty
Proptosis
Lagophthalmos
Sedation

Table 1: Causes of exposure.

Fungal infection has been described to cause 17% to 48% of corneal ulcers in tropical and subtropical regions in developing countries, compared with 1% to 5% in the United Kingdom, United States, and Australia. Natamycin has been reported to be effective against filamentous infections, such as *Fusarium* and *Aspergilus*; however, it is less effective against yeast infections, like *Candida sp.* for which amphotericin B has been the recommended treatment. Although there is no established gold standard treatment, in suspicion of fungal

keratitis, voriconazole is widely used in our environment as first option [5].

DM
Herpetic keratitis and other infections
Refractive surgery
Chronic use of contact lenses
V cranial nerve surgery
Radiotherapy

Table 2: Causes of neurotrophic disorders.

Materials and Methods

Case 1 was a 75-year-old woman with history of bilateral ptosis that had been treated with levator aponeurosis resection. After the surgery, there was a remaining entropion on the left eye that caused malocclusion, which led to corneal ulceration. Later, she underwent a second reconstructive surgical procedure with retroauricular skin and sclera grafts.

Afterwards, a central corneal infiltrate with satellite lesions appeared. A corneal scraping was performed, and the culture showed *Candida albicans*.

Initially, topical chlorhexidine and voriconazole were prescribed, but the latter was substituted by fluconazole due to intolerance. However, the infiltrate persisted.

Consequently, topical amphotericin B and nystatin and oral voriconazole were added during the process, which resulted in the decrease of the infiltrate and edema.

Artificial tears, autologous serum and a bandage contact lens were added for the concurrent corneal ulceration and thinning.

The infection remained active and the anterior segment OCT showed corneal thickness of 226 microns and distorted corneal structures despite the maximum medical treatment provided (Figures 1 and 2). At that moment we decided to add Cacicol 20® one drop every two days.

Case 2 was a contact lens wearer 39-year-old man who consulted for red eye and mild blurred vision in his right eye for 24 h. Anterior segment examination showed mild hyperemia and a central 3 mm corneal erosion with an infiltrate that reached the stroma. The anterior chamber was deep and there were no cells or fibrin in it (Figure 3). Corneal scraping was obtained for culture and antibiogram. Vancomycin (50 mg/ml) and ceftazidime (50 mg/ml) every hour were empirically prescribed.

4 days later, filamentous fungi were observed in the culture. Voriconazole and natamycin every hour were prescribed. 3 days later, the culture yielded *Fusarium spp*.

1 week later, the size of the infiltrate remained the same. Consequently, oral voriconazole 200 mg/12 h was added.

1 week later, the size of the infiltrate had decreased to 2 mm, but the epithelial defect persisted and corneal thickness was decreased. Artificial tears, autologous serum and a bandage contact lens were added.

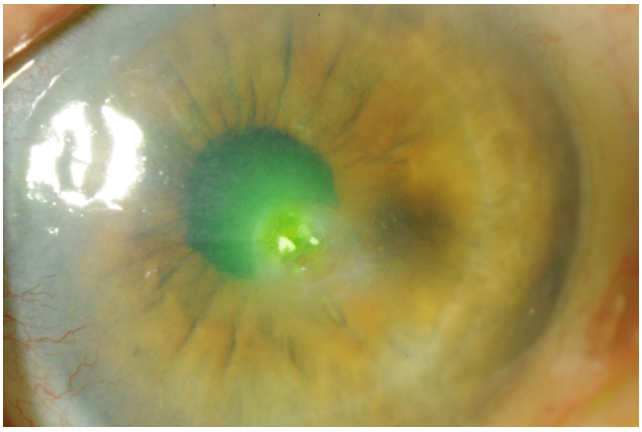

Figure 1: The cornea showing the active infection.

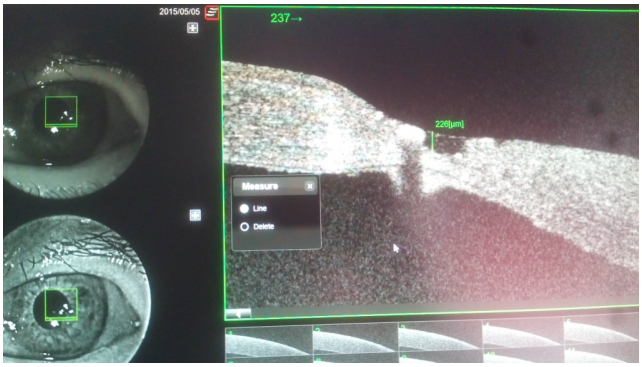

Figure 2: The anterior segment OCT showed corneal thickness of 226 microns and distorted corneal structures despite the maximum medical treatment provided.

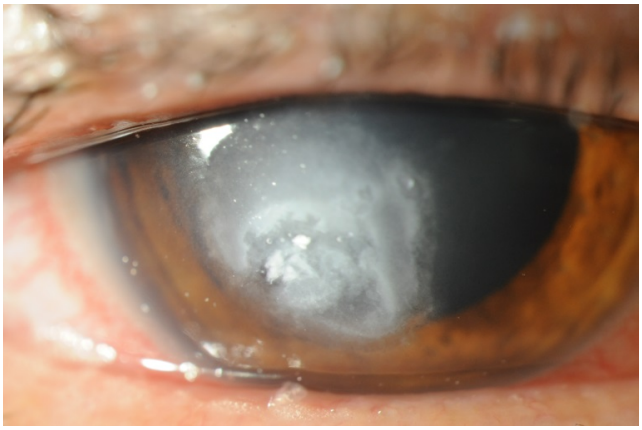

Figure 3: The anterior chamber deep with no cells or fibrin in it.

3 weeks later, the infiltrate was replaced by leukoma that did not exhibit signs of active infection, but the epithelial defect and the corneal thinning progressed. The anterior segment OCT showed then

descemetocele (Figure 4). At that moment, Cacicol 20® one drop every two days was added.

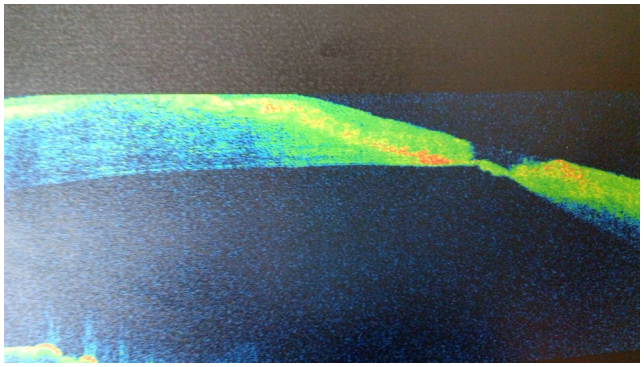

Figure 4: The anterior segment OCT showing the descemetocele during infection.

Results

In case 1, one week after starting Cacicol 20®, a central leukoma without signs of activity was observed (Figure 5) and the corneal thickness increased to 331 microns. After three weeks, the corneal thickness rose to 391 microns (Figure 6) and Cacicol 20® was withdrawn. Due to the favourable evolution, the antifungal treatment was slowly tapered. Three months later, a persistent central leukoma without any signs of infection was observed. The best corrected visual acuity was 0.1.

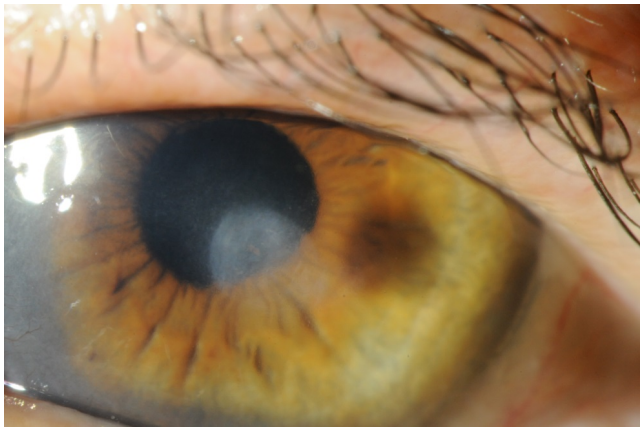

Figure 5: In case 1, One week after starting the treatment with Cacicol 20®, a central leukoma without signs of fungal activity was observed.

In case 2, three weeks after starting Cacicol 20®, complete epithelial healing was achieved (Figure 7) and the corneal thickness rose to 148 microns (Figure 8). Five weeks after starting Cacicol 20®, corneal thickness was 224 microns and Cacicol 20® was withdrawn then. The residual leukoma was paracentral, and the best corrected visual acuity with scleral contact lens was 0.8.

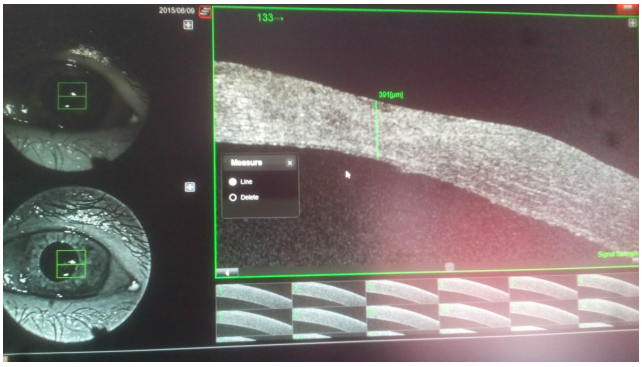

Figure 6: The corneal thickness increased from 331 microns and after three weeks, the corneal thickness rose to 391 microns.

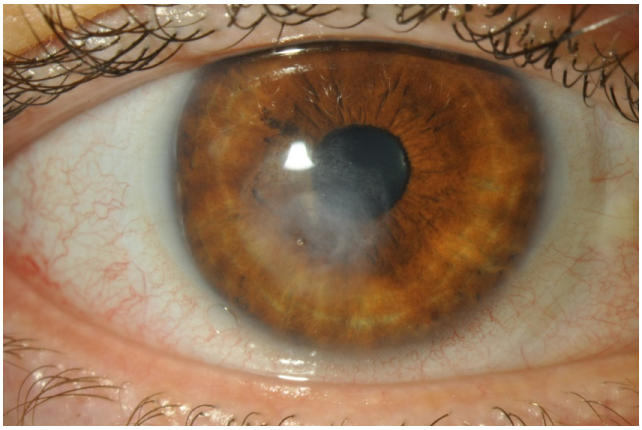

Figure 7: Case 2 representing the treatment of Cacicol 20® for 3 weeks shown the complete epithelial healing.

Discussion

The evidence supporting the treatment of fungal keratitis appears to be weak. There is no evidence to date that any particular drug, or combination of drugs, is more effective in the treatment of fungal keratitis in global terms. There are several drugs available, such as voriconazole, fluconazole, itraconazole, natamycin, clorhexidine, amhotericin B or sulphadiazine [6].

Concerning the treatment of *Candida keratitis*, amphotericin B and natamycin have proved equal effectiveness and full inhibition against *Candida keratitis* isolates, being the drug of choice for any species of *Candida*. For *Candida albicans*, vorizonazole reaches an inhibition rate of 77%, and fluconazole reaches only 7.7% [7].

The treatment was well tolerated in both cases, and no local or systemic side effects appeared.

In the case of *Fusarium keratitis*, natamycin reduces the risk of perforation and the need of therapeutic keratoplasty compared to voriconazole. Natamycin also proved more successful at clearing culture positivity, and achieved better visual acuity. Reepithelialization

time and infiltrate or scar size were not significantly different between the 2 treatments [8].

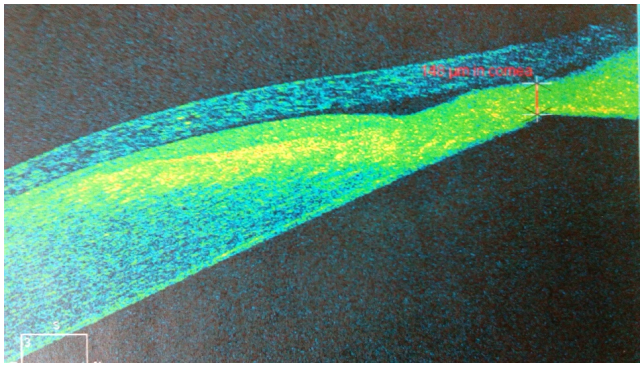

Figure 8: The anterior segment OCT showing the corneal thickness increase upto 148 microns.

For the management of persistent epithelial defects, the combination of a silicone-hydrogel lens and autologous serum eye drops can heal some cases that are refractory to treatment with silicone-hydrogel bandage contact lenses or autologous serum alone. However, this regimen is ineffective in other cases. [9].

Cacicol 20® one drop every two days in monotherapy proved to heal some cases of corneal ulceration that had been refractory to treatment with artificial tears. The mean time to healing was 8.7 weeks. However, it was ineffective in other cases [10].

The combination of a silicone-hydrogel bandage contact lens and one drop of Cacicol 20® every day achieved complete healing within 2 weeks in several cases of persistent corneal ulceration in relation to neurotrophic keratopathy, map-dot corneal dystrophy and penetrating keratoplasty. They were previously refractory to intensive medical treatment, including a silicon-hydrogel bandage contact lens, autologous serum and artificial tears [11].

Concerning persistent epithelial defects caused by infection, Cacicol 20® one drop every 2 days achieved complete healing within 3 weeks in a case of neurotrophic ulcer after keratitis by acanthamoeba. The ulcer was previously refractory to treatment with bandage contact lens, artificial tears and autologous serum [2].

We are reporting two cases of persistent corneal ulceration related to fungal keratitis. Case 1 suffered from persistent corneal ulceration due to exposure caused by palpebral retraction after ptosis surgery and enhanced by trophism disorders caused by Candida infection. The corneal ulceration was refractory to combined treatment with bandage contact lens, artificial tears and autologous serum. The infiltrate persisted despite maximum antifungal therapy. 3 weeks after Cacicol 20® every 2 days, the epithelial healing was complete and the corneal thickness rose from 226 to 391 microns (73% of the initial thickness). The infiltrate was replaced by a sterile leukoma. 4 months after withdrawing Cacicol®, the corneal thickness remained stable, there were no signs of infection and no deposits on the bandage contact lens were observed.

Case 2 suffered from persistent corneal ulceration caused by trophism disorders due to a Fusarium keratitis. He developed severe corneal thinning refractory to combined treatment with bandage contact lens, artificial tears and autologous serum. The infiltrate disappeared with maximum antifungal therapy, including oral voriconazole. 5 weeks after Cacicol 20® every 2 days, the epithelial healing was complete and the descemetocele progressed to 224 microns of corneal thickness.

Taking into account our cases and the commented studies, RGTA like Cacicol could be an effective option for persistent corneal ulcerations that are refractory to maximum conventional medical treatment (bandage contact lens and autologous serum), which would save surgical procedures. Moreover, based on our experience, they could be prescribed during active fungal infection without causing any side effects, despite the contraindication in case of active ocular infection that appears in the leaflet of Cacicol®. To the best of our knowledge, no cases have been published so far using Cacicol® on active fungal keratitis. Additional studies would be necessary to confirm these results.

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