# Management of herpes zoster neurotrophic ulcer using a new matrix therapy agent (RGTA): A case report\*

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#### **KEYWORDS**

Neurotrophic ulcer; Matrix therapy; Heparan mimetic; RGTA

**Summary**: Neurotrophic keratopathy is a potential consequence of herpes simplex virus (HSV) or varicella zoster virus (VZV) infection. The treatment is based on artificial tears and the withdrawal of preserved eye drops or other types of epithelial toxic topical medicines. Autologous serum or amniotic membrane transplantation may also be used in severe cases, but their cost and safety are still under debate. We report a case of a patient with a history of herpes zoster ophthalmicus, who developed a persistent epithelial ulcer after cataract surgery, with no improvement despite 3 weeks of artificial tears (eight drops per day). A new ophthalmologic solution based on a regenerating agent (RGTA, Cacicol20®) was then used, with a dosage of two eye drops per week for 6 weeks. Improvement was observed 1 week later, and complete healing was obtained in less than 3 weeks, with no side effects. This heparin mimetic, which may stimulate extracellular matrix healing, may be a possible alternative therapy to autologous serum or amniotic membrane transplantation in severe neurotrophic ulcer. However, randomised studies are necessary to validate this observation. © 2011 Elsevier Masson SAS. All rights reserved.

### Introduction

Neurotrophic keratitis, also called metaherpetic keratitis, is the consequence of partial or complete denervation of the cornea at the origin of a chronic degenerative condition of the corneal epithelium

[1]. Metaherpetic keratitis, consequence of an infection with HSV or VZV, is the most common cause of this [1-8]. The corneal hypoesthesia entails a reduction in the quantity of tears (reduction in the tearing reflex), and therefore their quality, by increasing their viscosity and their osmolarity, and a neurogenic inflammation by increasing the AmpC at the root of direct trophic problems [1]. This results in a significant change to the concentrations of pro-inflammatory molecules, which leads to an impairment of the corneal epithelial cells, with loss of microvilli and slowdown in their speed of renewal. The ultimate consequence is the appearance of chronic epithelial, then stromal, ulcers [9,10]. These epithelial and stromal conditions are often aggravated by the use of eye drops that are potentially toxic for the ocular surface (antiviral, antibiotic and anti-inflammatory eye drops, use of eye drops containing benzalkonium chloride) prescribed to treat a possible etiological cause, while the problem is essentially trophic.

The functional signs combine a significant reduction in vision, tearing and photophobia. The evolution can occur according to three stages: simple superficial punctate keratitis in the interpalpebral area (stage I), acute epithelial loss associated with stromal oedema (the edges of the epithelial deficit, initially smooth, curl up over time) (stage II), and lastly ulceration with stromal lysis and risk of corneal perforation (stage III) [2].

The therapeutic principles of the neurotrophic ulcer are firstly based on the cessation of any eye drops that are toxic for the ocular surface, i.e. in practice the cessation of eye drops with preservatives, and the withdrawal of topical antivirals or antibiotics. In general wetting agents are associated at a high dose, in order to dilute the inflammatory effectors and inhibitors of healing (metalloproteases) [1].

In stages II and III, diluted autologous serum or amniotic membrane transplantation are effective treatments. The limits of autologous serum are the difficulty of its manufacture (need for clean room preparation by a pharmacy department), and the risk of infection linked both to the method of preparation and the active principles (growth factors) contained in the preparation [11, 12]. The limits of AMT are the need to practise a surgical procedure, not to mention the cost of the graft and the operation [1, 13].

We are reporting the case of a patient treated for a neurotrophic ulcer after ophthalmic herpes zoster with a biodegradable tissue regeneration agent (Cacicol20®) that can serve as replacement, at least in first line treatment, for the two techniques previously described.

#### Observation

A patient aged 83, pseudophakia of the right eye, consulted his doctor in May 2009 for a reduction in visual acuity linked to a cataract of the left eye. In his ophthalmological history was the existence of age-related macular degeneration (AMD), bilateral but asymmetrical, with the right eve having suffered several neovascular episodes treated with anti-VEGF therapy, with considerable resulting Furthermore there was left ophthalmic herpes zoster having occurred several years atrophy. previously, relatively severe at the time of onset, having left areas of scleral atrophy on either side of the central meridian (Fig. 1). The postoperative follow-ups were marked by the discovery at the first postoperative visit of a huge epithelial ulcer (Fig. 2). Faced with the absence of spontaneous improvement in 48 hours and corneal hypoesthesia tested with a cotton tip, the diagnosis of herpes zoster neurotrophic ulcer was raised. The standard postoperative treatment was modified, with introduction of topical corticosteroid therapy (at rapidly reducing doses), combined with preservativefree wetting agents and vitamin A ointment. In spite of the elimination of all epithelial toxic topical treatments, the ulcer reduced only very little in the space of three weeks of treatment (Fig. 2). Treatment with a tissue regeneration agent (Cacicol20<sup>©</sup>) was then proposed, at the dosage of one drop twice a week, in addition to preservative-free wetting eye drops. A full ophthalmological examination was carried out on the third, seventh, 14<sup>th</sup>, 21<sup>st</sup>, 28<sup>th</sup> and 56<sup>th</sup> day postoperative. Under treatment, the ulcerated surface carrying the fluorescein reduced regularly (Fig. 3 and 4), and epithelial healing was complete between the second and third weeks of treatment (Fig. 5) (treatment continued for five

weeks in total). Greyish white opacification, sub-epithelial, persisted opposite the zone affected (Fig. 5), non-regressive under test treatment with preservative-free topical corticosteroids. The final visual acuity was limited to 5/10 Parinaud 3 three months after surgery, and has been stable since this date. The fundus oculi left still shows a slight atrophic AMD.

Figure 1. Scleral necrosis complicating ophthalmic herpes zoster

Figure 2. Neurotrophic keratitis resistant to wetting treatment (three weeks after cataract surgery)

Figure 3. Neurotrophic keratitis during healing (seven days after commencing treatment with Cacicol20®)

**Figure 4**. Almost healed neurotrophic keratitis (D14 after commencing treatment with Cacicol20®)

**Figure 5**. Complete healing (one month after commencing treatment with Cacicol20®); the persistence of greyish white opacification can be noted in the anterior stroma

Figure 6. The sub-epithelial nerves seem to stop at the scar

Figure 7. Sub-epithelial nerves of normal appearance located away from the scar

The confocal microscopic examination (Heidelberg® HRT) carried out after full healing of the ulcer, several months after the episode, showed an apparent cessation of the sub-epithelial nerve endings opposite the edges of the scar, but a normal appearance of these fibres away from this scar (Fig. 6 and 7). The central aesthesiometry, carried out in the same period as the confocal microscopic examination, showed identical values, although reduced, on both the right and the left (40mm at the Luneau<sup>TM</sup> Cochet-Bonnet aesthesiometer).

## Discussion

The symptoms presented by this patient fully illustrate one of the potential complications of ocular surgery and epithelial toxic treatments, notably eye drops containing benzalkonium chloride [14, 15] (corticosteroids, antibiotics, NSAIDs with preservatives) on a cornea formerly affected by severe ophthalmic herpes zoster.

Ophthalmic herpes zoster is accompanied by a reduction in the central corneal sensitivity in 21% of patients in the acute phase, and in 49% of them within the following year. This hypoesthesia persists for over a year in around one third of patients [7, 16, 17].

When it is very severe, corneal hypoesthesia can entail neurotrophic keratitis, the clinical nature of which can be limited to superficial punctate keratitis in the interpalpebral area or evolve towards a huge epithelial ulcer, even stromal lysis with risk of perforation [18]. In this observation, the degree of corneal sensitivity could have been evaluated precisely initially using the Cochet-Bonnet aesthesiometer, with the risk of ulceration being proportional to the degree of corneal hypoesthesia [1], and a microscopic analysis would probably have shown a structural alteration to the intracorneal nerve plexus responsible, more than the functional impairment, for the herpes zoster corneal hypoesthesia [19]. Surprisingly, the aesthesiometry carried out after recovery was identical, although reduced, in both eyes. This observation is supported by the appearance in confocal microscopy (Fig. 6 and 7) which shows a normal appearance of the sub-epithelial nerves outside of the scar zone, with this being sufficiently little extended to be selectively tested with the Cochet-Bonnet device. However, a comparative examination in confocal microscopy before and after treatment with Cacicol20® may have made it possible to specify the structural evolution of the epithelial nerves during the evolutionary process.

Treatment is based firstly on the withdrawal of all potentially epithelial toxic eye drops, particularly those containing preservatives. On the other hand, repeated instillations of wetting agents are proposed [10]. In the event of resistance, the two most commonly used alternatives are autologous serum and amniotic membrane transplantation. Their efficacy has furthermore been reported in

several types of severe impairment to the corneal surface, as in severe dry eye syndrome owing to Gougerot-Sjögren syndrome or graft versus host disease, or even in neuroparalytic keratitis [11, 20-23]. Autologous serum is prescribed at the dosage of one drop three times a day for a duration of three months, to be renewed according to the evolution, with its use often being limited owing to the different stages necessary for its preparation and the infectious complications that can occur under treatment [24].

Amniotic membrane transplantation is used in extreme cases (corneal perforation or pre-perforating condition), and in severe conditions of the ocular surface (Stevens-Johnson syndrome or chemical burns complicated by extensive limbic ischaemia) [25-27]. It makes it possible to reinforce the adhesion and the differentiation of the basal epithelial cells, to facilitate migration and to prevent epithelial cellular apoptosis [28]. Among the therapeutic arsenal for ocular surface pathologies it is also an effective treatment, however it requires fast access to an operating theatre which presents its own risks (infection notably).

Cacicol20® is an eye drop based on dextrans substituted with carboxymethyl, sulphate and hydrophobic groups, member of the family of tissue regeneration agents (RGTA). Their use was first proposed in skin healing after burns [29]. RGTAs, the therapeutic interest of which was described in 2005 by Papy Garci *et al* [30], are large biopolymers engineered to replace the heparan sulphates destroyed upon tissue injuries [30-33]. These complex sugars are usually specifically bound to extracellular matrix proteins and growth factors, and protect them from proteolysis. They recreate the extracellular microenvironment enabling migration and multiplication of the repairing cells [34-37]. Furthermore, RGTA inhibits *in vitro* the proteolytic enzymes such as elastases, plasmines and cathepsin G, reinforcing this aspect of *in vivo* protection of the matrix [38].

An initial non-controlled French pilot study showed the efficacy of RGTA in chronic corneal dystrophy and treatment resistant corneal ulcers, notably reducing pain and stimulating healing [38]. Corneal healing was obtained in the majority of patients presenting a corneal ulcer (four patients out of five) with very good local and general tolerance (no infectious episode reported), with however a relapse of the ulcer in two of them soon after stopping treatment. This study was based on a dosage of a single weekly drop, and concluded that a higher dosage could be more effective. The conclusion of this pilot study led us to propose, in our particular case, the application of two drops per week. This dosage made it possible to observe the onset of significant healing from the seventh day, and to obtain total closure of the epithelial ulcer in a little over two weeks. The patient did not describe pain or burning upon instillation, and no adverse effect was observed.

This new type of ophthalmic preparation seems to be an interesting alternative solution to autologous serum and to amniotic membrane transplantation in treatment resistant neurotrophic ulcers. It presents the interest of a low dose (it would seem that a dosage of one drop twice a week is preferable), and apparently very good local and general tolerance. However, a comparative study with the reference treatments would make it possible to detect the correct indications more precisely, and thus eventually define the official rules for its use, which is for the moment outside of the scope of the AMM.

## **Declaration of interests**

The authors declare they have no conflict of interest in connection with this article.

## References