

Evaluation of a new matrix regenerating agent in patients with Sjögren syndrome and superficial ulcerative keratitis resistant to conventional therapy

A report of 3 cases

Franck Fajnkuchen, MD^{a,b}, Denis Barritault, PhD^c, Audrey Giocanti-Aurégan, MD, PhD^{a,d,*}

Abstract

Rationale: Sjögren syndrome (SS) is frequently associated with ulcerative keratitis, which is difficult to treat due to lacrimal tear deficiency and inflammation of the ocular surface.

Patient concerns: We report the successful additive effect of a matrix regenerating agent (RGTA, Cacicol) in SS patients with severe superficial ulcerative keratitis resistant to conventional therapy.

Diagnoses: Retrospective, noncomparative case series of patients with primary or secondary SS associated with chronic diffuse keratitis.

Interventions: All patients (3 women, aged 46, 59, and 84 years) had several years of dry-eye disease history and recurrent keratitis despite having used maximal dose topical therapies including artificial tear substitutes, topical vitamin A, and cyclosporine 0.05% emulsion. All patients suffered from dry, diffuse, and chronic superficial keratitis of at least 75% of the corneal surface, with no sign of corneal neovascularization or opacity.

Outcomes: RGTA treatment led to a rapid and marked decrease of ocular pain, burning, irritation, foreign body sensation, and improvement of visual acuity. Total diffuse keratitis healing occurred after several months of treatment. Discontinuation of RGTA administration led to the recurrence of severe keratitis; re-introduction of RGTA was successful. No local or systemic adverse effects related to treatment were reported.

Lessons: RGTA treatment was effective and safe in this small series of 3 patients suffering from SS associated with recurrent or chronic superficial ulcerative keratitis resistant to conventional therapy.

Abbreviations: CREST syndrome = the acronym CREST refers to the five main features: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, KCS = keratoconjunctivitis sicca, LE = left eye, NEI = National Eye Institute, RE = right eye, RGTA = matrix regenerating agent, SPK = superficial punctate keratitis, SS = Sjögren's syndrome, VAS = visual analog scale.

Keywords: corneal ulcer, dry eye, keratitis, RGTA, Sjögren syndrome

Editor: N/A.

Disclosure of any funding received for this work: This work was supported by Laboratoires Théa, Clermont-Ferrand, France

Conflict of interest statement: Dr Fajnkuchen is a consultant for Allergan, Bayer, and Novartis; Dr Audrey Giocanti-Aurégan is a consultant for Allergan, Alimera, Bayer, Novartis, and Optos Plc.

Reprint request: Ophthalmology Department, Avicenne Hospital, DHU Vision and Handicaps, APHP, Paris 13 University, Bobigny, France. E-mail: audrey.giocanti@aphp.fr Phone: +33148955815.

The authors have no conflicts of interest to disclose.

^aOphthalmology Department, Avicenne Hospital, DHU Vision and Handicaps, APHP, Paris 13 University, Bobigny, ^bCentre d'Imagerie et de Laser, Paris, ^cParis Est University, Creteil, ^dCRRET CNRS U 4971, Paris, France.

* Correspondence: Audrey Giocanti-Aurégan, Ophthalmology Department, Avicenne Hospital, DHU Vision and Handicaps, APHP, Paris 13 University, Bobigny, France (e-mail: audrey.giocanti@aphp.fr).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2018) 97:10(e9935)

Received: 12 December 2017 / Accepted: 29 January 2018

http://dx.doi.org/10.1097/MD.00000000000009935

1. Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by exocrine gland dysfunction due to infiltration of inflammatory cells.^[1] Dry eye from SS is a multifactorial disease that results in lacrimal functional unit dysfunction. Patients with SS have more severe ocular features and chronic inflammation than patients without SS, especially conjunctival and corneal staining.^[2–4] In this context, diffuse keratitis may occur and lead to chronic pain and visual impairment.

Treatment of keratoconjunctivitis sicca (KCS) in patients with SS should aim to prevent or reduce corneal damage, improve re-epithelialization, stop progressive corneal ulceration, and address inflammation and tear restoration. The wound healing process of most epithelial corneal defects is normally rapid and self-limited. In the event of severe dry-eye disease such as in SS, painful keratitis may be slow to heal despite maximal dose; treatment with conventional therapy including artificial tear substitutes, topical vitamin A, and cyclosporine emulsion.^[5] There are currently few treatment options in case of nonhealing ulcers or chronic keratitis and none of them are commercially available.

The medical product Cacicol is a matrix regenerating agent (RGTA) containing poly-carboxymethylglucose sulfate, a

heparan sulfate analog. This product is available as a preservative-free ophthalmic solution that promotes healing of chronic corneal lesions such as persistent epithelial defects, and epithelial corneal dystrophy with associated pain. Research has shown that this polymer replaces the naturally damaged heparan sulfate at the site of injury, restores the matrix architecture, protects heparin-binding growth factors and matrix proteins from proteolysis, and preserves the natural microenvironment of the cells and the endogenous factors that promote tissue regeneration.^[6] Complete corneal healing has previously been shown in a series of patients with resistant corneal ulcers, including neurotrophic ulcers.^[7] Here we report the successful relief of symptoms and healing of refractory diffuse chronic keratitis after RGTA treatment in patients with SS.

2. Materials and methods

Clinical charts of 3 patients with SS (according to the European criteria^[8]) and diffuse chronic epithelial keratitis treated with RGTA eye drops (Laboratoires Théa, Clermont-Ferrand, France) were retrospectively reviewed in the Ophthalmology Department at Avicenne Hospital, Bobigny, France). Patients already under maximal dose—local therapy received additionally 1 drop of RGTA every other day. RGTA was prescribed in the context of the UNICOL study (CT08L06UC) that was approved by the French ethical committee. This study was conducted in accordance with the principles of the Declaration of Helsinki and informed consent was obtained from all patients. All information regarding ocular history including treatments and corneal healing was collected. Corneal staining was assigned to each of 5 corneal areas (superior, nasal, central, inferior, temporal) and scored using the National Eye Institute (NEI) scale^[9] (maximum total score of 15).

3. Results

3.1. Case 1

A 46-year-old female patient was diagnosed with primary SS in 2004 and treated since that time for bilateral dry-eye syndrome. In 2010, she experienced an exacerbation of her symptoms and exhibited painful epithelial keratitis in the right eye (RE) refractory to conventional topical therapy including carmellose eye drops (5 drops/day), sodium chloride eye drops (5 drops/day), topical vitamin A (1 drop/day), and 0.05% cyclosporine eye drops (1 drop/day), and oral minocycline. She complained of constant photophobia and ocular pain rated as 8/10 on a 10 cm visual analog scale (VAS) in the RE. Ocular burning and foreign body sensation in the RE were also reported as frequent. Visual acuity in the RE was reduced (20/40 vs 20/20 in the left eye). In the RE, there was no sign of hyperemia or chemosis, blepharitis and meibomitis were mild, the Schirmer test showed no tears (unmoistened strip) after 5 minutes, and the corneal staining score (NEI) was 13/15. The RE keratitis was superficial and diffuse with a size of 8×5.5 mm and no sign of corneal opacity or dystrophy. The contralateral eye showed mild, nondiffuse, and superficial punctate keratitis (SPK). The RE was treated with 1 drop of RGTA every other day in addition to the previous treatment. The patient was seen 1 week later, after having instilled a total of 3 drops of RGTA, and ocular pain was already considerably improved (rated as 1/10), with no need for oral analgesics. Other subjective symptoms also improved including burning sensation after 1 month, and irritation and foreign body

sensation after 2 months of treatment. Visual acuity of the RE also improved to 20/32 after 7 days and was totally recovered (20/20) after 1 month. Partial healing of the keratitis was observed after 2 months of treatment with a size of 4×4 mm associated with total recuperation of visual acuity. At that time (2 months of follow-up), the patient still complained of chronic photophobia, but no longer had any burning or pain and foreign body sensation was rare. Further improvement was observed after 3 months with an ulcer size of 4×1.3 mm. The corneal ulcer was totally healed after 6 months without any recurrence. At 5 years after the exacerbation of symptoms, the patient was still receiving RGTA treatment in addition to saline solution (5 drops/day), Vitamin A, and carbomer eye drops (2 drops/day), but cyclosporine had been discontinued. There were no functional symptoms and RGTA treatment was reduced to 1 drop every 3 days. No adverse event was noted over 60 months of RGTA use.

3.2. Case 2

An 84-year-old female patient was diagnosed with SS secondary to CREST syndrome in 1995. She had been known in our department for open-angle glaucoma treated with timolol since 1999, and underwent cataract surgery of both eyes in 2004. Dry-eye syndrome was diagnosed in 2005 and meibomitis had been treated with oral minocycline (100 mg/day) since 2010. The last ocular treatment in both eyes included physiological serum (4 drops/day), carbomer eye drops (4 drops/day), vitamin A (1 drop/day), and cyclosporine 0.05% (2 drops/day) initiated in 2005. In September 2010, the patient was referred for severe ocular pain (rated as 10/10 on the VAS). A Schirmer test was performed, showing a value of 3 mm/5 min for the RE and 10 mm/5 min for the left eye (LE). The break-up time (BUT) was 4 seconds in the RE and 5 sec in the LE. The patient also complained of constant photophobia, frequent ocular irritation and burning sensation. The corrected visual acuity was low in both eyes (20/80 [RE] and 20/63 [LE]). There was moderate chemosis. Eyelid examination showed mild meibomitis. Corneal staining score in the RE was 8/15. The epithelial keratitis was superficial with a size of 7.8×2.8 mm at baseline, with no corneal neovascularization, no corneal opacity, and normal corneal sensitivity. RGTA treatment (1 drop every 2 days) was initiated in the RE in addition to the previous ocular treatment. Ocular pain was reduced after 7 days of treatment (3/10 on the VAS) and we observed a decrease of ocular irritation and burning sensation after 1 month. Only photophobia remained constant during RGTA treatment. Corrected visual acuity of the treated eye improved to 20/32. Partial corneal keratitis improvement was observed after 1 month (7.2×2.2 mm) and 3 months (5.3×2.5 mm) of treatment. The patient was lost to follow-up until May 2012 when she was referred for severe dry-eye symptoms and recurrence of severe keratitis with mucous corneal filament after discontinuation of RGTA treatment in January 2012. The reintroduction of RGTA was successful, leading to an improvement in symptoms and a reduction of SPK. No adverse event was noted over 17 months of RGTA use.

3.3. Case 3

A 62-year-old female patient had primary SS confirmed in 1990. History of dry eye and corneal keratitis was recorded since 2004 and had been treated with polyvinilic acid/povidone eye drops (Refresh) (3 drops/day), an ocular preservative-free cationic emulsion (Cationorm) (3 drops/day), hyaluronic acid eye drops

(Vismed) (3 drops/day), sodium chloride artificial tears (10 drops/day) and topical cyclosporine 0.05% (2 drops/day). Blepharitis and meibomitis had been treated with oral minocyclin (100mg/day) since November 2007. A Schirmer test result was 0mm/5 min and the break-up time was 3 seconds for both eyes. In September 2010, the patient was referred for persistent ocular symptoms including irritation, burning, photophobia, and foreign body sensation in the RE. Ocular pain in the RE was rated as 9/10 on the VAS. Visual acuity was reduced in both eyes (20/40). Moderate chemosis of the RE was observed. Eyelid examination showed severe blepharitis and mild meibomitis. Corneal staining was graded as 8/15 and extended keratitis was diagnosed (8.0×4.1mm) with diminished corneal sensitivity. RGTA treatment (1 drop every 2 days) was initiated in addition to the previous ocular treatments. Except photophobia, which persisted over time, a decrease of other ocular symptoms including ocular pain (reduced to 6/10 on the VAS), and burning and foreign body sensation was observed after 1 month of treatment, and visual acuity improved (20/25 in the RE). Worsening of pain and keratitis was observed after 2 months (8.0×5.2mm) and 3 months (8.0×5.0mm) of RGTA treatment. The corneal keratitis size remained stable and superficial, without neovascularization and corneal opacity. RGTA treatment was maintained. Complete keratitis improvement was observed 1 year after RGTA introduction (September 2011). Cyclosporine 0.05% was stopped in March 2012 and preservative-free cationic emulsion in January 2013 when the KCS had been stabilized. In December 2014, the patient spontaneously interrupted RGTA treatment, and recurrence of symptoms were observed with filamentous keratitis covering 50% of the right cornea. RGTA treatment was resumed, but the patient was lost to follow-up. No adverse event was noted over 50 months of RGTA use.

4. Discussion

There are currently limited recommended treatment options for severe superficial corneal ulcers or keratitis when conventional therapies have failed. Conventional therapies are intended to provide only symptomatic relief and few target the pathophysiology of dry-eye disease. Topical cyclosporine emulsion has been investigated for the treatment of ocular surface disorders that may have an immune-based inflammatory component, and is an essential therapeutic innovation in the treatment of KCS in patients with SS.^[10] Lack of efficacy is, however, not uncommon particularly in chronic severe dry-eye disease.^[11] Other treatment options have been shown to promote the corneal re-epithelialization process, but these treatments may be difficult to initiate and have been shown to have poor therapeutic outcomes: autologous serum instillation can be of use in providing essential growth factors for wound healing^[12] but its use is limited due to the need for regular blood processing by specialized clinical laboratories, and amniotic membrane transplantations carry the potential risk of central scarring and are thus a second or third line treatment option when topical treatments have failed.

RGTA is a new treatment approach based on matrix regeneration activity to facilitate corneal wound healing. This heparan-mimicking product has been shown to be effective in treating chronic corneal ulcers such as neurotrophic keratitis^[7] and, more recently, in correcting persistent epithelial defects when used with bandage soft contact lenses.^[13] When applied on the ocular surface, RGTA replaces damaged heparan sulfates both as an extracellular scaffold element and as a protector of the matrix proteins and growth factors that it binds, hence restoring

conditions that mimic the initial extracellular matrix microenvironment.^[14] Compared to conventional treatment, RGTA has a long retention time since its elimination occurs during the natural extracellular matrix remodeling process of tissue repair.^[15] Thus, it is not necessary to instill more than one drop every 2 or 3 days, which is particularly convenient when patients already need to instill numerous other eye drops.

To our knowledge, this is the first report of corneal keratitis healing with RGTA treatment in patients with KCS associated with SS. Corneal ulcers in patients with SS are difficult to treat due to the chronic dry-eye disease and end-stage lacrymal deficiency despite cyclosporine eye drops. Moreover, these patients often have blepharitis and/or meibomitis, which contribute to the development of ocular inflammation and corneal damage.

In our case series, patients had severe lacrymal deficiency, several years of dry-eye history and chronic corneal keratitis. RGTA was successful in treating extensive superficial corneal keratitis with preserved corneal sensitivity. As reported previously,^[16] RGTA produces a rapid analgesic effect, which was apparent after the first instillations. This rapid effect could be due to the improvement of the extracellular matrix surrounding the sensitive nerve endings of the cornea. The constant affinity of RGTA to heparin binding growth factors and the heparin binding site of matrix proteins is in the nanomolar range^[17] and once applied to an injured matrix, binding of RGTA is expected to be immediate and irreversible. This pain relief effect lasted several hours or days and reoccurred when treatment resumed. This effect has previously been described^[16] as an increased time between administration and the recurrence of pain while healing. Even if a reduction of pain would be expected as healing progresses, the reversion of pain relief provides strong evidence of pain relief resulting exclusively from the product. In our case series, ocular symptoms, with the exception of photophobia, improved after several weeks of treatment, and was associated with partial or complete visual acuity recovery and a decrease in the size of keratitis. Corneal healing occurred more slowly in our case series than previously reported in patients with neurotrophic corneal ulcers.^[7] In 2 cases, partial corneal ulcer healing was observed within 3 months. In the last case, with severe recurrent blepharitis, a greater length of time was required to achieve a partial then complete response. This is in contrast with other case series of patients treated for neurotrophic ulcerative keratitis that showed total re-epithelialisation within 1 month in most cases (6/11 eyes).^[7] Such differences may be explained by the different pathophysiology of corneal keratitis and the wound-healing process between a neurotrophic and a systemic autoimmune disease.^[18] The recurrence of painful corneal keratitis after discontinuation of RGTA and with successful healing after re-introduction suggests that the corneal healing observed after several months of treatment cannot be attributed to the self-limited systemic autoimmune condition, but to the treatment per se. This indicates that RGTA treatment should not be discontinued in patients with severe ocular disease, especially since RGTA is well tolerated with no adverse events observed.

In conclusion, RGTA may be a useful treatment option for superficial keratitis in Sjögren's patients with severe dry-eye syndrome resistant to conventional therapy. Large controlled clinical studies are needed to rigorously evaluate this new treatment approach in this population.

Acknowledgments

This work was supported by Laboratoires Théa, Clermont-Ferrand, France.

References

- [1] Rasmussen A, Ice JA, Li H, et al. Comparison of the American–European Consensus Group Sjogren’s syndrome classification criteria to newly proposed American College of Rheumatology criteria in a large, carefully characterised sicca cohort. *Ann Rheum Dis* 2014;73:31–8.
- [2] Liew MSH, Zhang M, Kim E, et al. Prevalence and predictors of Sjogren’s syndrome in a prospective cohort of patients with aqueous-deficient dry eye. *Br J Ophthalmol* 2012;96:1498–503.
- [3] Goto E, Matsumoto Y, Kamoi M, et al. Tear evaporation rates in Sjögren syndrome and non-Sjögren dry eye patients. *Am J Ophthalmol* 2007;144:81–5.
- [4] Horwath-Winter J, Berghold A, Schmut O, et al. Evaluation of the clinical course of dry eye syndrome. *Arch Ophthalmol* 2003;121:1364–8.
- [5] Jeng BH. Treating the nonhealing epithelial defect. *Cataract Refract Surg Today Europe* 2011;6:25–8.
- [6] Cejkova J, Olmiere C, Cejka C, et al. The healing of alkali-injured cornea is stimulated by a novel matrix regenerating agent (RGTA, CACI-COL20): a biopolymer mimicking heparan sulfates reducing proteolytic, oxidative and nitrosative damage. *Histol Histopathol* 2014;29:457–78.
- [7] Aifa A, Gueudry J, Portmann A, et al. Topical treatment with a new matrix therapy agent (RGTA) for the treatment of corneal neurotrophic ulcers. *Invest Ophthalmol Vis Sci* 2012;53:8181–5.
- [8] Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren’s syndrome: a revised version of the European criteria proposed by the American–European Consensus Group. *Ann Rheum Dis* 2002;61:554–8.
- [9] Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. *CLAO J* 1995;21:221–32.
- [10] Donnenfeld E, Pflugfelder SC. Topical ophthalmic cyclosporine: pharmacology and clinical uses. *Surv Ophthalmol* 2009;54:321–38.
- [11] Dastjerdi MH, Hamrah P, Dana R. High-frequency topical cyclosporine 0.05% in the treatment of severe dry eye refractory to twice-daily regimen. *Cornea* 2009;28:1091–6.
- [12] Pan Q, Angelina A, Marrone M, et al. Autologous serum eye drops for dry eye. *Cochrane Database Syst Rev* 2017;2:CD009327.
- [13] Kymionis GD, Liakopoulos DA, Grentzelos MA, et al. Combined topical application of a regenerative agent with a bandage contact lens for the treatment of persistent epithelial defects. *Cornea* 2014;33:868–72.
- [14] Brignole-Baudouin F, Warnet JM, Barritault D, et al. RGTA-based matrix therapy in severe experimental corneal lesions: safety and efficacy studies. *J Fr Ophtalmol* 2013;36:740–7.
- [15] Barritault D, Gilbert-Sirieix M, Rice KL, et al. RGTA® or ReGeneraTing Agents mimic heparan sulfate in regenerative medicine: from concept to curing patients. *Glycoconj J* 2017;34:325–38.
- [16] Chebbi CK, Kichenin K, Amar N, et al. Pilot study of a new matrix therapy agent (RGTA OTR4120) in treatment-resistant corneal ulcers and corneal dystrophy. *J Fr Ophtalmol* 2008;31:465–71.
- [17] Rouet V, Meddahi-Pellé A, Miao H-Q, et al. Heparin-like synthetic polymers, named RGTAs, mimic biological effects of heparin in vitro. *J Biomed Mater Res A* 2006;78:792–7.
- [18] Liu KC, Huynh K, Grubbs J, et al. Autoimmunity in the pathogenesis and treatment of keratoconjunctivitis sicca. *Curr Allergy Asthma Rep* 2014;14:403.