

Treatment with Regenerating Agent Cacicol®

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The importance of extracellular matrix (ECM) integrity in maintaining normal tissue function is demonstrated by numerous pathologies of acute or chronic injury associated with destruction or disruption of its components. Regenerating agent therapy (RGTA) showed a strong anti-oxidative and protective effect resulting in reduced inflammation in chronic periodontitis, corneal lesions, oral and skin ulcers [1-5]. Two cases of corneal healing with Cacicol®. The first one was a chemical corneal burn with persistent lesions which resulted in restitutio ad integrum after treatment with Cacicol®. The second case was a contact lens wearer whose cornea had an ulcer with profuse lesions within the stromal layer and the evolution under conventional treatment for 2 weeks was insignificant and after the use of Cacicol® the lesions improved. Cacicol® is an innovative treatment that can be used in non-healing corneal lesions, eg: unresponsive corneal burns with conventional treatment.

Keywords: extracellular matrix (ECM), regenerating agent therapy (RGTA), corneal lesions, Cacicol®

The extracellular matrix (ECM) is a network of macromolecules that includes structural proteins, enzymes and soluble factors, which interact with surrounding cells, in order to maintain tissue structure and homeostasis.

The properties of regenerating agent therapy (RGTA) permit the reconstruction of the ECM, restoring biochemical and structural functions, and facilitating the processes of tissue regeneration and repair.

Preclinical studies demonstrate the efficacy of RGTA in acute or chronic oral ulcers, oral mucositis, as well as its potential as a skin protector following radiotherapy [1,2]. RGTA reduced bone loss to a hamster chronic periodontitis, leading to the restoration of alveolar bone and the regeneration of a periodontal ligament [3-5].

RGTA is already used in clinics in two commercially available products (OTR4120, alpha1-6 polycarboxyl-methylsulfate glucose), CACIPLIQ for the treatment of chronic skin lesions, and CACICOL for the treatment of corneal lesions.

The modern regenerating agent therapy represents the first ophthalmic matriceal therapy and an alternative to what usually would be an ophthalmic surgical case. The use of Cacicol® is beneficial in a wide variety of corneal lesions. The evidence of corneal healing through RGTA is evident in current clinical practice.

Painful and non-responding corneal lesions to conventional treatment serves as a continuous challenge in the clinic scene. The avascular corneal tissue have different and more complex wound healing mechanism than that in vascular tissues of the human body. The following pathologies all alter the corneal surface and release inflammatory mediators; Autoimmune keratitis, dry eye syndrome and chemical/traumatic lesions [6,7].

Persistent defects of the cornea is a clinical challenge for the ophthalmic specialist and stromal extracellular matrix (ECM) defects front high risk factors for cecity.

Our body cells are in a constant state of change. Tissue homeostasis act as a biological law whose action exists due to cellular signals among cytokines and extracellular matrix growth factors. These viability maintaining mechanisms are vulnerable to tissue lesions followed by scar over time. The extracellular matrix rehabilitation favors the regeneration of the injured tissues. Glycossaminoglycans and especially heparin-sulphates promote the intercellular communication. The French Academic team has demonstrated that mammals have the ability to regenerate by restoring the proper cellular micro-environment [8]. Heparin-sulphates are the key to cellular restoration and the RGTA have the potential of mimicking the destroyed heparin sulphates to replace them. These RGTAs aren't degraded by glycans and thus can attach themselves to the matrix proteins, ensuring the protection of these and the reconstruction of extracellular matrix.

Experimental part

Material and methods

Two cases of painful ocular surface lesions in which we achieved successful results only after the use of a topical regenerating agent, Cacicol®.

Written informed consent was obtained from these two patients for the treatment and publication of this report.

The first case was about a 31-year-old man with corneal chemical burn with an unknown substance (spray). Clinically, there was a central corneal ulcer within the superficial stroma.

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The second case was a 35-year-old man, contact lens wearer who appeared in the ophthalmology department with ocular pain, photophobia and decreased vision, symptoms secondary to a long trip which instituted poor personal hygiene. The visual acuity was very low, the patient's visual acuity was only hand movements. The biomicroscopic evaluation demonstrated a profound corneal ulcer with a risk of perforation. The pathogen of staphylococcus into the patients conjunctival secretions was identified.

Results and discussions

To the first patient the conventional treatment did not lead to the expected results, the epithelialisation was slow (3 weeks) and the stromal defect persisted. The use of a tissue regenerating agent administration - Cacicol®, one drop/week, lead to the remodeling of the cornea and to restitutio ad integrum. The visual acuity progressed from 0.1 at the beginning of treatment, to 1.0 after the cessation of treatment.

To the second patient the local treatment administered was Netilmycin for 10 days, hourly for 48 hours and then every 3 hours for 7 days. Because there were stagnant secretions, the treatment was switched to Vigamox for 7 days, Tobrex ointment and Indocollir for the inflammation.

When the secretions disappeared, re-epithelisation like Thealoz duo and Corneregel were administered. The scar was severe, that is why the RGTA were administered, one drop of Cacicol® per week for 5 weeks. The result was total epithelialization after 2 weeks. Figures 1 and 2 demonstrate the favorable evolution of the scar.

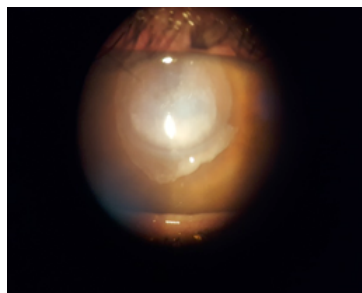


Fig. The aspect of the cornea before the treatment with Cacicol



Fig. 2. The aspect of the cornea after the treatment with Cacicol

There was insignificant evolution to conventional treatment in these cases, so, the therapeutic alternative to favor and ameliorate the scar was the Cacicol® matrix therapy. The chronic inflammatory component was associated with the lesion. Pain relief was alleviated after 2 weeks under the new RGTA's treatment with the restoration of the extracellular matrix which surrounds the sensitive nerve endings onto the cornea. The restitutio ad integrum was gained at the end of the therapy in the first case. In the second case, the improvement in visual acuity was 80% and the patient did not have any pain. The superior and paracentral parts of the cornea remain leukomic, under supervision.

The new therapeutic class of RGTA is a new and different promising healing agent from any product on the current

market and their innovation consist in creating a new micro-environment because of their content in heparin-sulphates [8].

The idea of recreating a new micro-environment due to the heparin-sulphates is a real innovation. RGTA's regeneration agents replace the degraded glycosaminoglycans such as heparin-sulphates and will furthermore settle on the matrix proteins and are resistant to the remodeling enzymes because they are not destroyed by proteolytic enzymes such as heparinases, thus providing protection for the stromal extracellular matrix environment and other components involved in tissue healing [9].

The RGTA's attached to the matrix proteins will allow the growth factors and cytokines to act on the injured area leading to the restoration of the matrix comparable to physiological conditions.

Heparin-sulphate and their analogues obstruct in vivo the proteolytic enzymes like elastase, plasmin, cathepsin G [10,11].

RGTA's have the potential of healing chronic wound problems of the entire body [12]. In order to promote epithelial wound healing, they contour a bio-skeleton which will activate cell adhesion and will be ready for the adhesion of growth factors onto the surface. RGTA's job is to link different structural proteins such as collagen, elastin and fibronectin, thus assisting in the formation of the corneal matrix architecture and can also restore the intercellular communication for the normal tissue regeneration, thus providing a strong mechanical protection for degradation. By this way, restoration of ECM (stromal extracellular matrix) scaffolding properties and process take place and the RGTA's reestablish the micro-environment.

Thus, this bio-skeleton being made, the micro-environment is just perfect to promote the healing through re-epithelialization and to secure the stromal extracellular matrix plan which will alleviate the pain. An anti-fibrotic response is done by decreasing the synthesis of collagen type III, decreasing the tissue edema and inflammation and reforming the collagen reorganization [13].

Oral mucositis is a complication of cancer treatment. Chemotherapy and radiation treatment cause oral mucosal atrophy and ulcerations, increasing the risk of infection and affecting the quality of life. RGTA prevented mucositis in 50% of treated hamsters and significantly reduced the mean lesion volume in the remaining animals [2].

Conclusions

The conventional treatment given in both cases did not lead to the expected results, which warranted new RGTA treatment, Cacicol®, which was introduced and the improvement of the lesion was immediate and evident through the alleviation of the pain and the evolution of the scar. Cacicol® was very well tolerated, did not have any local or general allergic reaction, nor side effects. The intraocular pressure remained within normal values and the ulcer did not relapse.

There are a variety of cases described in the literature which confirm their ability of restoring favourable corneal matrix healing process [9,14].

RGTA by its mode of action, its glucose-based structure, its ability to specifically localize to sites of injury where it is retained throughout the restoration process, and its natural elimination as a matrix element with no evidence of toxicity, makes it a safe product [15-17].

RGTA controls ocular surface inflammation and enhances corneal healing. As a result, RGTA's are the best choice to use for long lasting corneal lesions [18-21].

Studies demonstrate that RGTA matrix based therapy is an efficacious and non-invasive approach to treat various injuries affecting the cornea, muscle injuries, acute or chronic ulcers, oral mucositis, reduced bone loss in chronic periodontitis [18-25].

References

1. MANGONI M, YUE X, MORIN C, VIOLOT D, FRASCOGNA V, TAO Y, et al. Differential effect triggered by a heparan mimetic of the RGTA family preventing oral mucositis without tumor protection. *Int. J. Radiat. Oncol. Biol. Phys.* 2009;74(4):1242-50
2. MORVAN FO, BAROUKH B, LEDOUX D, CARUELLE J-P, BARRITAU D, GODEAU G, et al. An engineered biopolymer prevents mucositis induced by 5-fluorouracil in hamsters. *Am. J. Pathol.* 2004;164(2):739-46
3. ESCARTIN Q, LALLAM-LAROYE C, BAROUKH B, MORVAN FO, CARUELLE JP, GODEAU G, et al. A new approach to treat tissue destruction in periodontitis with chemically modified dextran polymers. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* 2003;17(6):644-51
4. LALLAM-LAROYE C, ESCARTIN Q, ZLOWODZKI A-S, BARRITAU D, CARUELLE J-P, BAROUKH B, et al. Periodontitis destructions are restored by synthetic glycosaminoglycan mimetic. *J. Biomed. Mater. Res. A.* 2006;79(3):675-83
5. LALLAM-LAROYE C, BAROUKH B, DOUCET P, BARRITAU D, SAFFAR J-L, COLOMBIER M-L. ReGeneraTing agents matrix therapy regenerates a functional root attachment in hamsters with periodontitis. *Tissue Eng. Part A.* 2011;17(17-18):2359-67
6. BAUDOIN C. A new approach for better comprehension of diseases of the ocular surface. *J. Fr. Ophthalmol* 2007;30:239-46
7. BAUDOIN C. The pathology of dry eye. *Surv. Ophthalmol* 2001;45(Suppl):11-20
8. BARRITAU D, GARCIA FILIPE S, ZAKINE G. Les bases de la thérapie matricielle en médecine régénérative par les RGTA: du fondamental à la chirurgie plastique annales de chirurgie plastique esthétique (2010)55,413-420
9. LEDOUX D, MERCIRIS P, BARRITAU D, CARUELLE JP. Heparin-like dextran derivatives as well as glycosaminoglycans inhibit the enzymatic activity of human cathepsin G. *FEBS* 2003;537:23-9
10. MEDDAHI A, LEMDIJABAR H, CARUELLE JP, BARRITAU D, HORNEBECK W. FCF protection and inhibition of human neutrophil elastase by carbomethyl benzylamidesulfonated dextran derivatives. *J Biol Macromol* 1996;18:141-5
11. BARRITAU D, CARUELLE JP. Regenerating agents (RGTA): a new therapeutic approach. *Ann Pharm Fr.* 2006;64(2):135-144
12. GROAH SL, LIBIN A, SPUNGEN M, NGUYEN KL, WOODS E, NABILI M, RAMELLA-ROMAN J, BARRITAU D. Regenerating matrix-based therapy for chronic wound healing: a prospective within-subject pilot study. *Int Wound J.* 2011;8(1):85-95
13. CEJKOVA J, OLMIERE C, CEJKA C, TROSAN P, HOLAN V. The healing of alkali-injured cornea is stimulated by a novel matrix regenerating agent (RGTA, CACICOL20): a biopolymer mimicking heparan sulfates reducing proteolytic, oxidative and nitrosative damage. *Histol Histopathol.* 2014;29(4):457-478
14. ZAKINE G, BARBIER V, GARCIA-FILIPES, LUBOINSKI J, POPY-GARCIA D, CHACHQUES JC, CARPENTIER A, BARRITAU D. Matrix therapy with RGTA OTR4120 improves healing time and quality in hairless rats with deep second-degree burns. *Plast Reconstr Surg.* 2011;127(2):541-550
15. MEDDAHI A, BREE F, POPY-GARCIA D, GAUTRON J, BARRITAU D, CARUELLE J-P. Pharmacological studies of RGTA, a heparan sulfate mimetic polymer, efficient on muscle regeneration. *J. Biomed. Mater. Res.* 2002;62(4):525-31
16. CHAREF S, TULLIEZ M, ESMILAIRE L, COURTY J, POPY-GARCIA D. Toxicological evaluation of RGTA OTR4120, a heparan sulfate mimetic. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* 2010;48(7):1965-8
17. BARBIER CHASSEFIERE V. PhD Thesis: Synthèse, Activités Pro-Cicatricielles et Etude Pharmacologique de l'OTR4120, RGTA Mimétique des Glycosaminoglycannes. Université Paris-Est Créteil (2008).
18. GUMUS, K., GOMAS, G.M., HOMEM DE MELO, M.S., BARRITAU D., KARAKUCÜK, S. A new matrix therapy agent (RGTA) for faster corneal healing and less ocular discomfort following epithelial accelerated corneal crosslinking in progressive keratoconus. *J. Refract. Surg.* (2016)
19. KYMIONIS GD, LIAKOPOULOS DA, GRENTZELOS MA, DIAKONIS VE, KLADOS NE, TSOULNARAS KI, et al. Combined topical application of a regenerative agent with a bandage contact lens for the treatment of persistent epithelial defects. *Cornea.* 2014;33(8):868-72
20. RENAULT D, LAZREG S, ABDELLAH MB. The use of matrix therapy in the treatment of corneal perforation. *Invest. Ophthalmol. Vis. Sci.* 2015;56(7):720-720
21. CHEBBI CK, KICHENIN K, AMAR N, NOURRY H, WARNET JM, BARRITAU D, et al. Pilot study of a new matrix therapy agent (RGTA OTR4120) in treatment-resistant corneal ulcers and corneal dystrophy. *J. Fr. Ophthalmol.* 2008;31(5):465-71
22. DE MONCHY I, LABBÉ A, POGORZALEK N, GENDRON G, M'GARRECH M, KASWIN G, et al. Management of herpes zoster neurotrophic ulcer using a new matrix therapy agent (RGTA): a case report. *J. Fr. Ophthalmol.* 2012;35(3):187.e1-6
23. ZAKINE G, LE LOUARN C. First applications of matrix therapy in plastic and aesthetic surgery. *Ann. Chir. Plast. Esthet.* 2010;55(5):421-8
24. MEDDAHI A, ALEXAKIS C, POPY D, CARUELLE J-P, BARRITAU D. Heparin-like polymer improved healing of gastric and colic ulceration. *J. Biomed. Mater. Res.* 2002;60(3):497-501
25. MEDDAHI A, BENOIT J, AYOUB N, SÉZEUR A, BARRITAU D. Heparin-like polymers derived from dextran enhance colonic anastomosis resistance to leakage. *J. Biomed. Mater. Res.* 1996;31(3):293-7.

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