NEUROTROPHIC KERATOPATHY IN TYPE I FAMILIAL AMYLOIDOTIC POLYNEUROPATHY
- A NEW THERAPEUTIC APPROACH -

INTRODUCTION

Familial amyloidotic polyneuropathy (FAP) is a heterogeneous group of familial diseases characterized by systemic accumulation of amyloid fibrils in the peripheral nerves and other organs, including the eye. Knowledge of the biochemical nature of the amyloid fibril proteins in these hereditary syndromes is limited. FAP is classified in types I-IV, according to the different clinical features and geographic origin. FAP type I, firstly described by Corino de Andrade in 1952[1], is the most frequent type, appearing mainly in Portuguese, Japanese, Swedish, and Jewish families. It has its onset in the lower limbs and presents severe autonomic dysfunction affecting the cardiovascular and renal systems[2]. It is an autosomal dominant inherited disease characterized by abnormal production and extracellular deposition of transthyretin (TTR), a carrier protein of thyroxin in the plasma and vitamin A in the retina. More than 90% of this protein is synthesized in the liver, but there is evidence of ocular production by both retinal and ciliary pigment epitheliums[3]. Replacement of valine-30 by methionine in TTR is necessary for the formation of these amyloid deposits[4].

The cornea is one of the most highly innervated tissues of the human body, supplied by the long ciliary nerve, through the ophthalmic branch of the trigeminal nerve. This assures corneal sensation and provides trophic factors, essential in the maintenance of its structure and function, by regulating epithelial integrity, proliferation and wound healing[5,6]. Reduced or absent corneal sensitivity, spontaneous epithelial breakdown and impairment of corneal healing[6] characterize neurotrophic keratopathy (NK), a rare degenerative corneal disease, potentially sight threatening. It results from localized or systemic conditions affecting nerve function along its course and is frequently associated to herpes keratitis, chemical burns, long-term use of contact lenses, corneal surgery or ablative procedures for trigeminal neuralgia[7]. According to Mackie[8], clinical severity of NK is classified in 3 stages summarized in Table 1.

Table 1 – Mackie's Classification[8]

Stage	Clinical findings
I	Corneal epithelial hyperplasia and irregularity Superficial punctate keratopathy Increased viscosity of tear mucus and decreased break-up time
II	Persistent corneal epithelial defect - smooth and rolled edges Descemet's membrane folds and stromal swelling Anterior chamber inflammatory reaction with hypopyon (rare)
III	Corneal ulcer Corneal perforation Corneal stromal melting

There are many ocular features associated to FAP type I, including, among others, corneal alterations, vitreous opacification, secondary glaucoma, scalloped pupils, slower pupillary reflexes and anomalous conjunctival vessels. In the cornea, primary amyloid deposits damage the epithelium and stroma. Infiltration of the orbital nerves can cause progressive autonomic

neuropathy with decreased corneal sensitivity, keratoconjunctivitis sicca and NK. This, together with hyposecretion of tears due to lacrimal gland infiltration, leads to severe dry eye, which contributes to epithelial injury exacerbation, deregulated proliferation, and parakeratosis[4,9-12].

Once established, both acute and chronic inflammation may sustain progression of the corneal pathology[13].

Treatment of these corneal epithelial injuries with vitamins, collagenase inhibitors, anti-inflammatory agents, prophylactic topical antibiotic, artificial tears or bandage contact lenses is frequently poor or of transient efficacy. In severe cases, oral doxycycline, autologous serum, amniotic membrane transplantation, tarsorrhaphy or a conjunctival flap are employed alone or in combination[14]. However, successful modulation of the healing response is rarely accomplished.

A new promising topical drop has emerged to revolutionize NK treatment: the matrix ReGeneraTing Agent (RGTA, polycarboxymethyl glucose sulfate). It is a biopolymer designed to mimic the heparan sulphates bound to corneal extracellular matrix proteins, protecting them from proteolysis and enabling growth factors and cytokines to act on the injured site. RGTA restores the physiological matrix organization and cellular microenvironment, stimulating the regeneration process[15]. Clinical studies with this new agent were performed in animals[16] and humans[15,17,18], showing encouraging results in the treatment of corneal ulcers and dystrophies of various etiologies. However, no literature using this new agent in NK patients with FAP is available.

The aim of this case report is to present 3 patients with FAP type I and NK who were successfully treated with a new matrix-regenerating agent – the RGTA, polycarboxymethyl glucose sulfate.

CASE PRESENTATION WITH ILLUSTRATIONS AND FIGURES

CASE 1

The first patient is a 47-year-old male diagnosed with FAP at the age of 20, with predominantly peripheral sensorimotor polyneuropathy, autonomic dysfunction and infiltrative cardiac manifestations, who underwent liver transplantation 7 years after the diagnosis. Ocular manifestations started ten years later. Left eye (LE) and right eye (RE) posterior vitrectomy and cataract surgeries were performed. Neurotrophic corneal ulcer grade 2 in Mackie's classification[8] was diagnosed 2.5 months after cataract surgery, non-responsive to occlusion therapy, or preservative free eye lubricants. Total corneal anaesthesia was demonstrated by cotton tip test and corneal ulcer borders were debrided. RGTA eye drops were started, instilled in the morning, once a week. Neurotrophic ulcer area was calculated as proportion of the total corneal area, assessed by slit lamp photography, using an image analysis software (ImageJ®, version 1.47, Wayne Rasband Research Service Branch, National Institute of Mental Health, Bethesda, MD). Ophthalmological evaluation with anterior segment photography (Figure 1) was performed at days 1, 7, 14, 21 and 28. Corneal ulcer area decreased from 8.76% at the 1st day to 3.11% at the 7th day. In day 14, corneal ulcer area was 3.34% followed by 3.11% (21st day) and complete corneal healing was achieved until the 28th day. A total of 5 instillations were applied. After a follow-up period of 7 months, there was no recurrence of corneal ulcer despite no significant improvement in visual acuity (VA).

No systemic or local side effects were noticed and no pain or discomfort during drop instillation was reported.

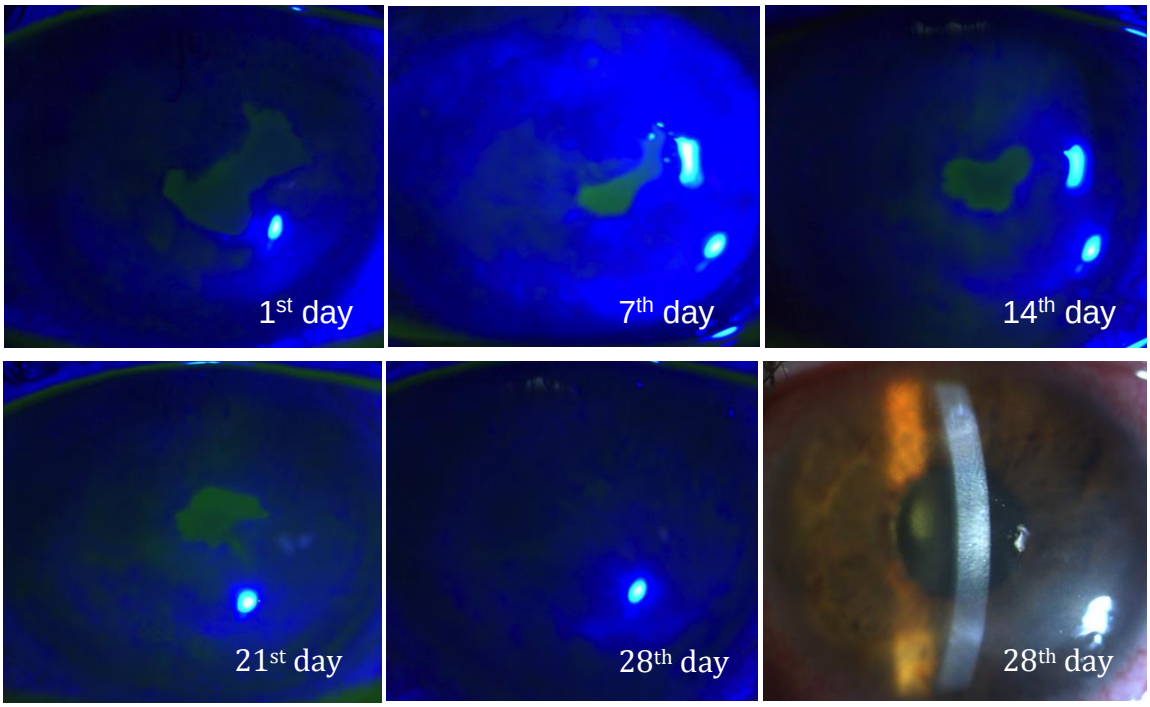

Figure 1 – Patient 1: anterior segment photography at days 1, 7, 14, 21 and 28 with fluorescein eye drop; without fluorescein eye drop at day 28.

CASE 2

A 54-year-old male was diagnosed with FAP type I and peripheral sensorimotor polyneuropathy, grade III atrioventricular block (pacemaker carrier) and renal insufficiency. Ocular history of central retinal vein occlusion of the RE, with no light perception, was known. Liver transplantation was performed at the age of 35. Ocular manifestations emerged 13 years after transplantation with LE secondary open-angle glaucoma, non-responsive to maximum topical treatment. A trabeculectomy followed by cataract surgery was performed in the LE. Neurotrophic corneal ulcer grade 2 in Mackie's classification[8] developed afterwards, non-responsive to occlusion therapy, or preservative free eye lubricants. Total corneal anaesthesia was demonstrated by cotton tip test and corneal ulcer borders were debrided. RGTA eye drops were started once a week. Ophthalmological evaluation with anterior segment photography (Figure 2) was performed at days 1, 7, 21 and 57. Corneal ulcer area decreased from 4.95% at the 1st day to 2.83% at the 7th day. On day 21, corneal ulcer area was 2.67% and two instillations per week were performed thereafter. Complete corneal healing was achieved until the 57th day. A total of 10 instillations were applied. After a follow-up period of 4 months, the patient presented no ulcer recurrence. Moderate corneal scarring occurred, with no significant improvement in VA noted. No systemic or local side effects were noticed and no pain or discomfort during drop instillation was reported.

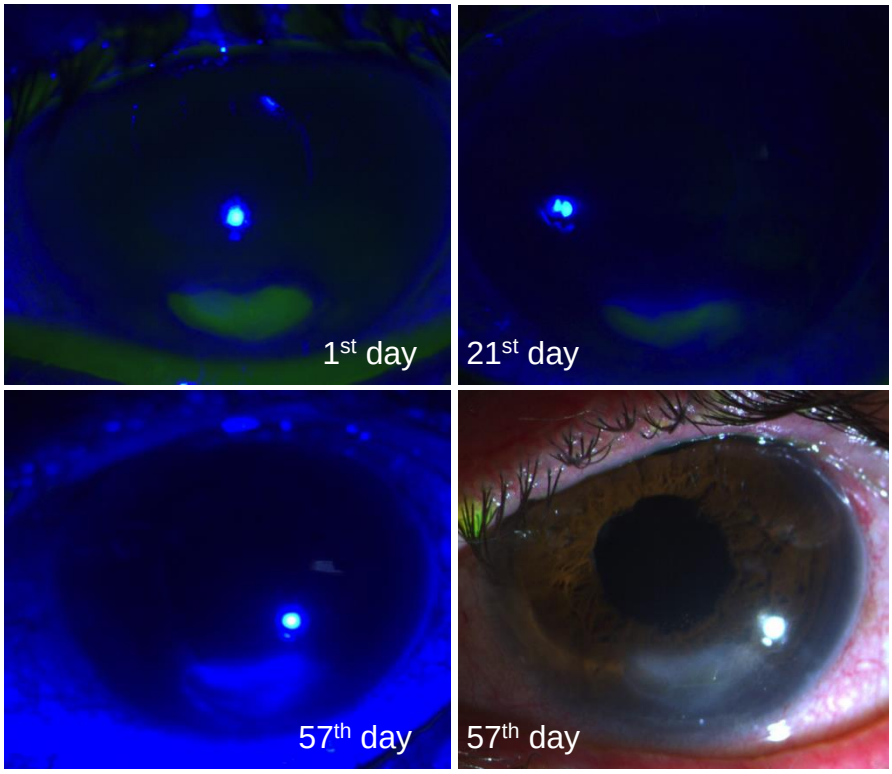

Figure 2 – Patient 2: anterior segment photography at days 1, 21 and 57 with fluorescein eye drop; without fluorescein eye drop at day 57.

CASE 3

The third patient is a 55-year-old female with FAP type I, presenting peripheral sensorimotor polyneuropathy and cardiac manifestations. She underwent liver transplantation at the age of 39. Ocular manifestations started 8 years after transplantation with posterior capsular amyloid deposition, secondary glaucoma, typical iris alterations and vitreous opacities on both eyes. Neurotrophic corneal ulcer grade 2 was diagnosed in the RE 6 weeks after cataract surgery. The ulcer was non-responsive to occlusion therapy, or preservative free eye lubricants. Total corneal anaesthesia was demonstrated by cotton tip test. RGTA eye drops were started, twice a week. Ophthalmological evaluation with anterior segment photography (Figure 3) was performed at days 1 and 14. Corneal ulcer area decreased from 19.10% at the 1st day to complete corneal healing until the 14th day. A total of 5 instillations were applied. After a follow-up period of 2 months, no recurrence was registered, with no significant improvement in VA.

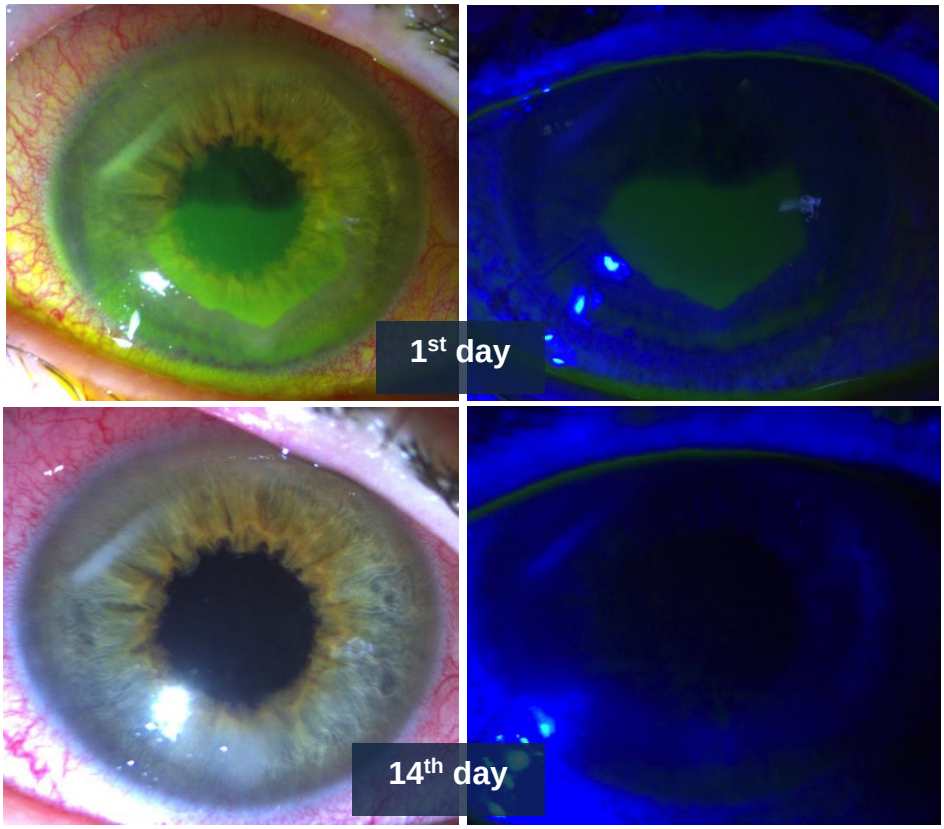

Figure 3 – Patient 3: anterior segment photography at days 1 and 14 without fluorescein eye drop (left images); with fluorescein eye drop at day 1 and 14 (right images).

DISCUSSION

Liver transplantation has been widely accepted as an effective therapy to halt systemic amyloid deposition because the precursor protein of amyloid deposits in tissues of FAP patients is predominantly synthesized by the liver. However, evidence of TTR small synthesis in both retinal and ciliary pigmented epithelium and choroid plexus[3] of the brain[19] has been found and cannot be prevented by liver transplantation[20]. Despite this surgery, all the 3 presented patients developed not only vitreous opacities, iris alterations and secondary glaucoma, but also decreased corneal sensitivity. These findings are in agreement with previous published reports of patients with FAP type-I submitted to liver transplantation[21].

Initially, formation of amyloid deposits in the cornea has a cytotoxic effect, damaging corneal sensory nerves, epithelium, and stroma. Corneal neuropathy associated with an impaired tear film promotes epithelial surface injury and disturbances in hydration and ionic homeostasis. Both persistent mechanical damage and cytotoxicity lead to tissue destruction and repeated attempts of wound healing[13].

Treating NK is not easy and remains a clinical challenge, particularly in FAP patients. In fact, none of the 3 patients responded to current conservative treatment. Few cases of NK patients with FAP are reported in the literature. Nonetheless, all presented severe hypoesthesia and keratoconjunctivitis sicca and culminated in bilateral corneal perforation[13,22], the last stage of NK that should be avoided at all cost.

The introduction of the new topical treatment for NK, the RGTA, polycarboxymethyl glucose sulphate, is a promising therapy to these patients. It belongs to the polysaccharides' family, derived from dextran by chemical substitutions with carboxymethyl, sulphate and hydrophobic groups[23,24]. This biopolymer is engineered to replace the heparan-sulphates destroyed upon tissue injury and to specifically bind extracellular matrix proteins and growth factors, protecting them from proteolysis[23].

Recent clinical studies already showed safety and effectiveness in treating NK in corneal dystrophies, resistant corneal ulcers[15] and after infectious keratitis[18], chemical burns and perforating keratitis[17], with mean wound healing ranging from 4 to 9 weeks.

The series here presented showed encouraging results: total re-epithelialization was achieved in all 3 patients within a mean period of 33 days (4.71 weeks) after initiating RGTA once/twice a week with no recurrence registered and a follow up time ranging from 2 to 7 months. These excellent results are reinforced by a larger series observed in the same department: 15 patients with various causes of NK and mean corneal ulcer area before treatment of 16,26%, treated with RGTA agent, showed complete corneal healing within a mean period ranging from 1 to 8 weeks. In these patients, treatment was started with one instillation per week. If no improvement in ulcer area was observed, two instillations were performed until complete corneal healing. Due to the limited sites for heparan binding available in the healing tissue, a perfectly well defined posology is not available, only the producer's recommendation of one/two weekly instillations.

CONCLUSION

Decreased corneal sensitivity, in patients with FAP type I, associated to an impaired tear production, can lead to NK development. The NK in these patients is one of the most challenging ocular surface pathologies. As these three patients were non-responsive to conservative NK topical treatment, a new substance, the RGTA, polycarboxymethyl glucose sulphate, was experimented. RGTA is easy to apply, and showed compelling effectiveness in corneal wound healing, being well tolerated by all patients.

These are the first cases of NK caused by FAP treated with RGTA. True potential of these eye drops was here demonstrated, showing that this approach might be an excellent solution to treat NK, even in this particular type of patients.

REFERENCES

1. Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. Brain, Sep 1952, 75(3), 408-427.
2. Lobato L. Classificação das amiloidoses. Sinapse. 2006; 6(1), 67-71.
3. Sandgren O. Ocular amyloidosis, with special reference to the hereditary forms with vitreous involvement. Surv Ophthalmol, Nov-Dec 1995, 40(3), 173-196.
4. Ando E, Ando Y, Okamura R, Uchino M, Ando M, Negi A. Ocular manifestations of familial amyloidotic polyneuropathy type I: long-term follow up. Br J Ophthalmol, Apr 1997, 81(4), 295-298.
5. Holland E, Mannis M, Lee WB. Neurotrophic Keratopathy. In *Ocular Surface Disease: Cornea, Conjunctiva and Tear Film.* Elsevier Health Sciences, 2013, p. 205-211.
6. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol, 2014, 8, 571-579.
7. Semeraro F, Forbice E, Romano V, Angi M, Romano MR, Filippelli ME, et al. Neurotrophic keratitis. Ophthalmologica, 2014, 231(4), 191-197.
8. Mackie IA. Neuroparalytic keratitis. In RF FRAUNFELDER F, MEYER SM, EDITORS. ed. *Current Ocular Therapy.* Philadelphia, PA, USA: WB Saunders, 1995.
9. Ando E, Ando Y, Maruoka S, Sakai Y, Watanabe S, Yamashita R, et al. Ocular microangiopathy in familial amyloidotic polyneuropathy, type I. Graefes Arch Clin Exp Ophthalmol, 1992, 230(1), 1-5.
10. Kawaji T, Ando Y, Nakamura M, Yamashita T, Wakita M, Ando E, et al. Ocular amyloid angiopathy associated with familial amyloidotic polyneuropathy caused by amyloidogenic transthyretin Y114C. Ophthalmology, Dec 2005, 112(12), 2212.
11. Monteiro JG, Martins AF, Figueira A, Saraiva MJ, Costa PP. Ocular changes in familial amyloidotic polyneuropathy with dense vitreous opacities. Eye (Lond), 1991, 5 (Pt 1), 99-105.
12. Lamkin JC, Jakobiec FA. Amyloidosis and the Eye. In *The eye and systemic diseases.* p. 4517-4533.
13. Dosso AA, Rungger-Brandle E. Bilateral corneal perforation in familial amyloidotic polyneuropathy. Graefes Arch Clin Exp Ophthalmol, Mar 2005, 243(3), 273-277.

14. Lambiase A, Rama P, Aloe L, Bonini S. Management of neurotrophic keratopathy. Curr Opin Ophthalmol, Aug 1999, 10(4), 270-276.
15. Chebbi CK, Kichenin K, Amar N, Nourry H, Warnet JM, Barritault D, et al. [Pilot study of a new matrix therapy agent (RGTA OTR4120) in treatment-resistant corneal ulcers and corneal dystrophy]. J Fr Ophtalmol, May 2008, 31(5), 465-471.
16. Brignole-Baudouin F, Warnet JM, Barritault D, Baudouin C. RGTA-based matrix therapy in severe experimental corneal lesions: safety and efficacy studies. J Fr Ophtalmol, Nov 2013, 36(9), 740-747.
17. Aifa A, Gueudry J, Portmann A, Delcampe A, Muraine M. Topical treatment with a new matrix therapy agent (RGTA) for the treatment of corneal neurotrophic ulcers. Invest Ophthalmol Vis Sci, Dec 2012, 53(13), 8181-8185.
18. De Monchy I, Labbe 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 Ophtalmol, Mar 2012, 35(3), 187.e181-186.
19. Soprano DR, Herbert J, Soprano KJ, Schon EA, Goodman DS. Demonstration of transthyretin mRNA in the brain and other extrahepatic tissues in the rat. J Biol Chem, Sep 25 1985, 260(21), 11793-11798.
20. Ando E, Ando Y, Haraoka K. Ocular amyloid involvement after liver transplantation for polyneuropathy. Ann Intern Med, Nov 20 2001, 135(10), 931-932.
21. Rosa A, Quadrado MJ, Ferrão J, Marques I, Costa E, Murta JN. Manifestações oculares de polineuropatia amiloidótica familiar tipo I em doentes submetidos a transplante hepático. Oftalmologia, 2009, 33, 177-183.
22. Frossard JL, Donati G, Reymond JM. Portuguese amyloidosis: a case of spontaneous bilateral corneal perforation. Am J Med, Nov 1996, 101(5), 562.
23. Rouet V, Meddahi-Pelle A, Miao HQ, Vlodavsky I, Caruelle JP, Barritault D. Heparin-like synthetic polymers, named RGTAs, mimic biological effects of heparin in vitro. J Biomed Mater Res A, Sep 15 2006, 78(4), 792-797.
24. Barritault D, Caruelle JP. [Regenerating agents (RGTAs): a new therapeutic approach]. Ann Pharm Fr, Mar 2006, 64(2), 135-144.