ARCH SOC ESP OFTALMOL. 2020;xxx(xx):xxx–xxx

ARCHIVOS DE LA SOCIEDAD ESPAÑOLA DE OFTALMOLOGÍA

www.elsevier.es/oftalmologia

Original article

Management of corneal neurotrophic ulcers with Cacicol®-RGTA (ReGeneraTing Agent): a case series☆

L. Salazar-Quiñones[a,b,*], *M. Molero-Senosiáin*[a], *S. Aguilar-Munoa*[a,c], *J.A. Gegúndez-Fernández*[a], *D. Díaz-Valle*[a], *A.M. Muñoz-Hernández*[a], *J.M. Benítez-del-Castillo*[a]

[a] *Unidad de Superficie e inflamación ocular, Departamento de Oftalmología, Hospital Clínico San Carlos, Madrid, Spain*
[b] *Departamento de Oftalmología, Hospital General Universitario de Ciudad Real, Castilla la Mancha, Spain*
[c] *Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom*

ARTICLE INFO

Article history:
Received 7 January 2020
Accepted 6 April 2020
Available online xxx

Keywords:
Cacicol®
RGTA
ReGeneraTing agent
Neurotrophic keratitis
Corneal ulcers

ABSTRACT

Purpose: Neurotrophic corneal ulcers are difficult to treat and the conventional treatment often results in failure. A new matrix regenerative agent ("ReGeneraTing Agents", RGTA), Cacicol® (Laboratoires Théa), has demonstrated good results over the last years. Therefore, the aim of this study was to evaluate the response to Cacicol® in a series of cases with corneal ulcers neurotrophic.

Methods: Retrospective case series. 11 patients with corneal ulcers unresponsive to conventional therapy underwent treatment with Cacicol®. One cycle included 1 drop every two days for 5 days.

Results: The range of conventional therapy prior to Cacicol® was 0–91 days. Upon introducing Cacicol® 82% (9/11) of the cases were cured and 18% (2/11) failed requiring an amniotic membrane transplant or penetrating keratoplasty. 67% (6/9) of the patients who had experienced healing required only one cycle of Cacicol®. 45% (5/11) patients needed more than one cycle of Cacicol®. One corneal bacterial ulcer responded favorably and one case related to *Acanthamoeba* failed. Most of the patients improved or maintained their visual acuity.

Conclusion: Cacicol® was a useful therapy in a high number of difficult neurotrophic corneal ulcers, including corneal infections. Some cases may require more than one cycle of Cacicol® or its immediate use to achieve the desired result.

☆ Please cite this article as: Salazar-Quiñones L, Molero-Senosiáin M, Aguilar-Munoa S, Gegúndez-Fernández JA, Díaz-Valle D, Muñoz-Hernández AM, et al. Manejo de las úlceras corneales neurotróficas con CACICOL®-RGTA (ReGeneraTing Agent): serie de casos. Arch Soc Esp Oftalmol. 2020. https://doi.org/10.1016/j.oftal.2020.04.015

* *Corresponding author.*
E-mail address: malisq2014@gmail.com (L. Salazar-Quiñones).

Manejo de las úlceras corneales neurotróficas con CACICOL®-RGTA (ReGeneraTing Agent): serie de casos

Palabras clave:
Cacicol®
RGTA
ReGeneraTing agent
Queratitis neurotrófica
Úlceras corneales

RESUMEN

Objetivo: Las úlceras corneales neurotróficas son difíciles de tratar y las terapias convencionales fracasan con frecuencia. Un nuevo agente regenerativo de la matriz extracelular ("ReGeneraTing Agents", RGTA), Cacicol® (Laboratoires Théa), ha demostrado buenos resultados en los últimos años. El objetivo de este estudio fue evaluar la respuesta a Cacicol® en una serie de casos con úlceras corneales neurotróficas.

Métodos: Serie de casos retrospectiva. 11 pacientes con úlceras corneales neurotróficas que no respondieron a una terapia convencional fueron tratados con Cacicol®. Un ciclo incluyó 1 gota cada 2 días durante 5 días.

Resultados: El rango de duración de la terapia convencional, previa al comienzo del tratamiento con Cacicol®, fue 0 a 91 días. Tras introducir Cacicol® el 82% (9/11) de los casos se curaron y el 18% (2/11) no lo hicieron, llegando a requerir un trasplante de membrana amniótica o una queratoplastia penetrante, respectivamente. El 67% (6/9) de los pacientes curados requirieron solo un ciclo de Cacicol® y el 45% (5/11) pacientes necesitaron más de un ciclo. Un caso de úlcera corneal bacteriana respondió favorablemente pero un caso infectado por Acamthamoeba fracasó. En la mayoría de los pacientes, la agudeza visual mejoró o se mantuvo.

Conclusión: Cacicol® resultó una terapia exitosa en una alta proporción de úlceras neurotróficas, incluidas las infecciosas. Algunos casosrequieren más de un ciclo de Cacicol® o su uso como primer línea de tratamiento.

Introduction

Management of corneal lesions such as epithelial defects or ulcers are frequently a challenge for ophthalmologists. Any delay in beginning treatment or a wrong therapeutic orientation could give rise to important complications including corneal opacity or even perforation with ensuing visual acuity and quality of life impairment.[1,2] Corneal repairs depend on adequate corneal innervation and the action of growth factors that regulate the process. In the course thereof, basal epithelial and limbus layer cells proliferate and migrate towards the damaged area, with stromal keratinocytes transforming into myofibroblasts and generating extracellular matrix (ECM) to restore corneal tissue. However, the production of ECM is deficient in kerathan sulfate proteoglycans and this alters the distribution of collagen and the architecture of ECM, with the result of corneal opacity.[3,4]

Treatment for neurotrophic ulcers such as autologous serum, artificial tears, collagenase inhibitors, vitamins, prophylactic topical antibiotics, anti-inflammatory agents or therapeutic contact lenses are in some cases not enough. Accordingly, it could become necessary to bring in surgical therapies such as temporary or permanent tarsorraphy, conjunctival flap, amniotic membrane transplant or keratoplasty, all of which are more expensive and not risk-free.[3,5] For this reason, other treatments are in development including the use of autologous plasma enriched with platelet-derived growth factors, epidermic and fibroblastic.[6]

An additional alternative therapy is Cacicol® (OTR4120; Laboratoires Théa, Clermont-Ferrand, France) that belongs to the family of ReGeneraTing Agents (RGTA®). Cacicol® is a heparan sulfate glycosaminoglycan, which has been utilized for treating corneal ulcers and dystrophies as well as neurotrophic keratopathy.[7,8] Heparan sulfate is a key component of ECM and plays an important role in tissue homeostasis, avoiding ECM degradation and enabling the accumulation and stabilization of growth factors that are able to bond to heparin, thus facilitating tissue repair.[4,9]

Several studies in animal models have demonstrated the efficiency of topical treatment with Cacicol® for corneal ulcers, specifically its potential neuro-regeneration effect,[4] its ability to improve corneal haze after Excimer laser surgery and its ability to reduce oxidative and proteolytic damage.[10,11]

Even though very few studies have been conducted in humans, several studies described the potential epithelization benefits of Cacicol® after corneal cross-linking in keratocone[12] or after trans-epithelial ablation laser surgery in myopic patients[9] and in the improvement of neurotrophic ulcers[3,8,13] or persistent epithelial defects (PED) after bacterian keratitis.[14] In a non-controlled prospective study no benefits of treatment with Cacicol® were observed in 4 of 6 eyes with neurotrophic ulcer.[15] In what concerns corneal infections, very few studies have utilized Cacicol® as a treatment in these cases.[3,5] Accordingly, the objective of this study was to describe a case series of neurotrophic corneal ulcers, including 2 cases of infectious ulcers, and evaluate response to treatment with Cacicol®.

Methods

A retrospective case series conducted at the San Carlos Clinic Hospital of Madrid, Spain. Between January 2014 and December 2017, 16 patients were administered treatment with Cacicol®. Five patients were discarded because they did not have complete clinic history in the follow-up, leaving 11 patients in the study. The Helsinki declaration on ethical discipline for medical research in humans was complied with, and the study was approved by the ethical committee of the San Carlos Clinic Hospital. In addition, patients signed respective informed consents.

The neurotrophic ulcers diagnosis was conducted on the basis of clinic criteria by experts in the ocular surface area in accordance with the Mackie classification.[16] Patients had been unsuccessfully treated with conventional therapy. One cycle of treatment with Cacicol® consisted in one drop (0.33 mL) in the morning at 2-day intervals during 10 days, totaling 5 drops. The timing of the introduction of Cacicol®, the number of cycles applied (between 1 and 4) and termination of treatment were decided by the specialist according to the complexity of the case and the characteristics of the patient.

A patient was considered to be at risk with previous history of recurring PED and positive response to Cacicol® or history of poor response to previous conventional treatment.

Demographic data, anamnesis, slit lamp examination, visual acuity, follow-up photographs, previous treatments and duration thereof, time elapsed since starting treatment with Cacicol® up to healing or failure, the number of applied cycles and the interval in days between applied cycles were obtained from patients clinic records.

The results were classified as "improvement" if the ulcer diminished in size, "failure" if the ulcer size remained the same or increased, and "healing" if the defect closed entirely. The follow-up of ulcers was through slit lamp biomicroscopy by several observers.

In addition to Cacicol®, all patients were administered adjuvant treatment in accordance with standard clinic practice comprising preservative-free artificial tears, 20% autologous serum, topical or systemic antibiotics, topic or systemic corticoids or oral vitamins. After healing no information was collected. Statistical analysis was based on proportions.

Results

Out of the 11 cases with neurotrophic keratopathy, 18% (3/11) exhibited PED and 82% had stromal corneal ulcers. Four cases were post-herpetic, one associated to cicatricial pemphigoid, one post-surgery (vitrectomy), one secondary to facial paresis, one on penetrating keratoplasty (PKP), one associated to bacterian keratitis on bullous keratopathy, one with mixed infectious Acanthamoeba and fungal keratitis secondary to the use of contact lenses, and one in an immunosuppressed patient being treated with Everolimus after kidney transplant.

Age range of patients was from 25 to 96 years. Fig. 1 shows corneal ulcer images before and after treatment with Cacicol®. Other characteristics can be found in Table 1. Patients were administered conventional treatment for a variable period of time between zero and 91 days, with an average of 31.7 days. Two risk patients were administered treatment with Cacicol® at baseline without having received previous alternative therapy.

The majority of patients (82%, 9/11) were classified as "healed" and 18% (2/11) as "failure". Mean time to healing was 24.9 days with a range of 10–60 days. In 67% (6/9) of healed patients only one cycle of Cacicol® was utilized. In this group, 4 cases were cured 10 days after beginning treatment and the other 2 were cured between 18 and 31 days later. A further 3 healed patients received more than one cycle of Cacicol®, 2 of them were given to cycles of Cacicol® and were cured at 30 and 60 days after the first day of therapy, respectively, with the time interval between the first and second cycle was between 0 and 4 days. The third patient that required more than one cycle exhibited an infected ulcer that required 3 successive cycles of the drug without intervals and exhibited improvement at the end of each cycle, and reached healing 45 days after the beginning the first cycle.

Conventional treatment time prior to Cacicol® therapy and treatment time with Cacicol® up to healing varied for each patient. Cases 1, 2 and 11 summarized in said table received 91, 61 and 21 days of conventional therapy without success, respectively, but resolved 10 days after beginning treatment with Cacicol®. Cases 4, 7 and 10 received 25, 17 and 7 days of conventional therapy and were resolved at 45, 60, and 18 days after beginning treatment with Cacicol®, respectively. Cases 3 and 8 who were administered Cacicol® at baseline were cured after 30 and 10 days from beginning treatment, respectively (Table 1).

In what concerns the 2 failures, case 5 was secondary to infectious keratitis by Acanthamoeba and filamentous fungi and was administered 4 cycles of Cacicol® with intervals between 1 and 43 days between cycles and finally needed amniotic membrane transplant. Case 9 was a patient with systemic immunosuppression that received 2 cycles of Cacicol® separated by 15 days and finally needed penetrating keratoplasty.

In 63% of patients (7/11), visual acuity remained the same or improved. The remaining 4 patients had no visual acuity documentation. Autologous serum at 20% was used in 82% (9/11) of patients. No adverse effects related to Cacicol® therapy were observed.

Discussion

In some cases, conventional treatment of corneal lesions is insufficient, making it necessary to consider alternatives.[17] The introduction of the RGTA® or «regenerative agent» family, that includes Cacicol® provides an additional step in the therapeutic algorithm that has shown positive results in several series.[3,7,8] However, the literature does not include data on the use of successive cycles of Cacicol® or its early use in selected high risk cases. In addition, very few authors have published the results of its use in infectious corneal ulcers.[5,14]

In the present series, Cacicol® has shown good results with healing of 82% (9/11) of cases, while visual acuity remained the same or improved in most patients. Even though several studies confirmed these findings, reporting between

Table 1 – Characteristics of patients with unhealed corneal ulcers who received treatment with Cacicol®.

Patient nr. gender, age (years)	Diagnostic	VA/ulcer size/days of conventional therapy prior to Cacicol®	Therapy before and during treatment with Cacicol®	Cacicol® therapy: cycle number (1–4), results (healing time, final VA, outcome)
Patient 1. F, 70	Corneal ulcer. Post-herpetic neurotrophic keratopathy	VA FC. Size: 1.8 × 1 mm. 91 days	Topical: AT, AS 20%, medroxyprogesterone acetate. Systemic: valaciclovir, tetracycline, vitamin C.	Cycle 1: day 10. VA 0.05. Healing.
Patient 2. F, 61	PED post-vitrectomy for vitreous hemorrhage in RDP Antecedent: panretinophotocoagulation, Ahmed valve for neovascular glaucoma	VA FC. Size: 2.5 × 1.4 mm. 65 days	Topical: AT, AS 20%, erythromycin cream, tromicyna/quinolone, 5% sodium chloride, T-CL.	Cycle 1: day 10. VA FC. Healing.
Patient 3. F, 70	PED. Post-herpetic neurotrophic keratopathy. Antecedent: 2 previous corneal ulcers that received Cacicol and were cured. Pseudophakic	VA: UK. Size: 4.2 × 1 mm. 0 days	Topical: AT, AS 20%, nocturnal lubricating gel, quinolone, cyclopentolate, ganciclovir, gel (discontinued) Systemic: valaciclovir.	Cycle 1: day 22. linear erosion. Day 31. VA 0.1. Healing.
Patient 4. F, 96	Infected corneal ulcer (*Staphylococcus epidermidis*). Corneal abscess. Bullous keratopathy, IOL in anterior chamber	VA: MH. Size: 80% of the cornea. 25 days	Topical: AT, AS 20%, retinol ointment, quinolone, trimetropin-polymyxin/vancomycin, ceftazidime, voriconazole, ceftazidime, tropin, fluorometholone. Systemic: tetracycline, vitamin C	Cycle 1: day 7. size UK. Improvement. Interval between cycles 1 and 2: 0 days. Cycle 2: day 7. 4 × 5 mm. Improvement. Interval between cycles 2 and 3: 0 days. Cycle 3: day 10. 0.1 × 0.5 mm. Day 45. Healing.
Patient 5. F, 39	Infected corneal ulcer (Acanthamoeba, filamentous fungi). Keratocone, contact lens user. Hydrops, White cataracts, phacolytic glaucoma	VA FC. Size: 7 mm.	Topical: AT, AS 20%, polymyxin-neomycin-gramicyin, voriconazole, chlorhexidine, propamidine, atropin. Systemic: tetracycline, corticosteroids, acetazolamide, supplemented with potassium/ascorbic acid	Cycle 1: day 5. 5 mm. Day 10. Improvement. Interval between cycles 1 and 2: 1 day Cycle 2: day 14. small defect (UK). Improvement. Interval between cycles 2 and 3: 6 days

– Table 1 (*Continued*)

Patient nr. gender, age (years)	Diagnostic	VA/ulcer size/days of conventional therapy prior to Cacicol®	Therapy before and during treatment with Cacicol®	Cacicol® therapy: cycle number (1–4), results (healing time, final VA, outcome)
		44 days		Cycle 3: day 14. 70% defect of the entire cornea, phacolytic glaucoma. Failure. Interval between cycles 3 and 4: 43 days. Cycle 4: day 10. Failure. Two AMT. PKP and cataract surgery.
Patient 6. M, 76	PED. Calcium corneal deposits. Trichiasis. Cicatricial pemphigoid. Previous PED	VA 0.2.	Topical: AT, AS 20%, erythromycin ointment, fusidic acid, atropine, cyclosporine.	Cycle 1: day 15. defect increased (UK). Failure. Interval between cycles 1 and 2: 4 days
		Size: 2 × 2.5 mm.	Systemic: corticosteroids, calcium proton pump inhibitors	Cycle 2: day 12. VA 0.3. Day 30 Healing.
		67 days		
Patient 7. M, 83	PED. Neurotrophic keratopathy post-herpetic keratouveitis. Facial herpes zoster	VA 0.2.	Topical: AT, lubricant night gel, beta blockers, tobramycin, corticosteroids ointment and eyedrops, antiviral and erythromycin cream, cyclopentolate, T-CL.	Cycle 1: day 10. Defect diminished 60%. Improvement. Interval between cycles 1 and 2: 0 days.
		Size: UK.	Systemic: valaciclovir	Cycle 2: day 14. VA 0.3. small defect. Day 60 healing.
		17 days		
Patient 8. F, 63	PED. Neurotrophic keratopathy. Facial paresis due to acoustic neurinoma surgery. Tarsorrhaphy and gold weight in upper eyelid due to lagophthalmos	VA FC.	Topical: AT, AS 20%, erythromycin ointment, antiviral ointment, quinolone, nocturnal ocular occlusion.	Cycle 1: day 10 VA CF. Healing.
		Size: UK. 0 days		
Patient 9. F, 25	PED. Immunosuppressant therapy (Everolimus) for kidney transplant. Arterial hypertension	VA 0.1.	Topical: AT, AS 20%, erythromycin ointment, cyclopentolate, quinolone.	Cycle 1: day 10. 1 mm. Improvement. Day 26. 3 × 1 mm. Interval between cycles 1 and 2: 15 days.
		Size: 1.5 × 2.5 mm	Systemic: tetracycline	Cycle 2: day 10. VA 0.1. defect increased. Failure. AMT.
		12 days		
Patient 10. M, 89	PED. Post-herpetic neurotrophic keratopathy.	VA 0.1.	Topical: AT, ceftazidime and fortified vancomycin, cyclopentolate.	Cycle 1: day 10 small defect. Day 18 VA 0.1. Healing.

– Table 1 (*Continued*)

Patient nr. gender, age (years)	Diagnostic	VA/ulcer size/days of conventional therapy prior to Cacicol®	Therapy before and during treatment with Cacicol®	Cacicol® therapy: cycle number (1–4), results (healing time, final VA, outcome)
		Size: 2.4 mm.	Systemic: doxycycline, vitamin C	
		7 days		
Patient 11. M, 55	PED. Neurotrophic keratopathy. Antecedent: PKP, endothelitis due to cytomegalovirus	UK	Topical: AT, AS 20%, ganciclovir gel.	Cycle 1: size UK. Day 10. Healing.
		21 days	Systemic: valganciclovir	

VA: visual acuity; FC: finger counting; PED: persistent epithelial defect ; AT: artificial tears without preservatives ; T-CL: therapeutic contact lens; IOL: intraocular lens; MH: movement of hands ; PKP: penetrating keratoplasty; RDP: proliferative diabetic retinopathy; AS: autologous serum; AMT: amniotic membrane transplant; UK: unknown.

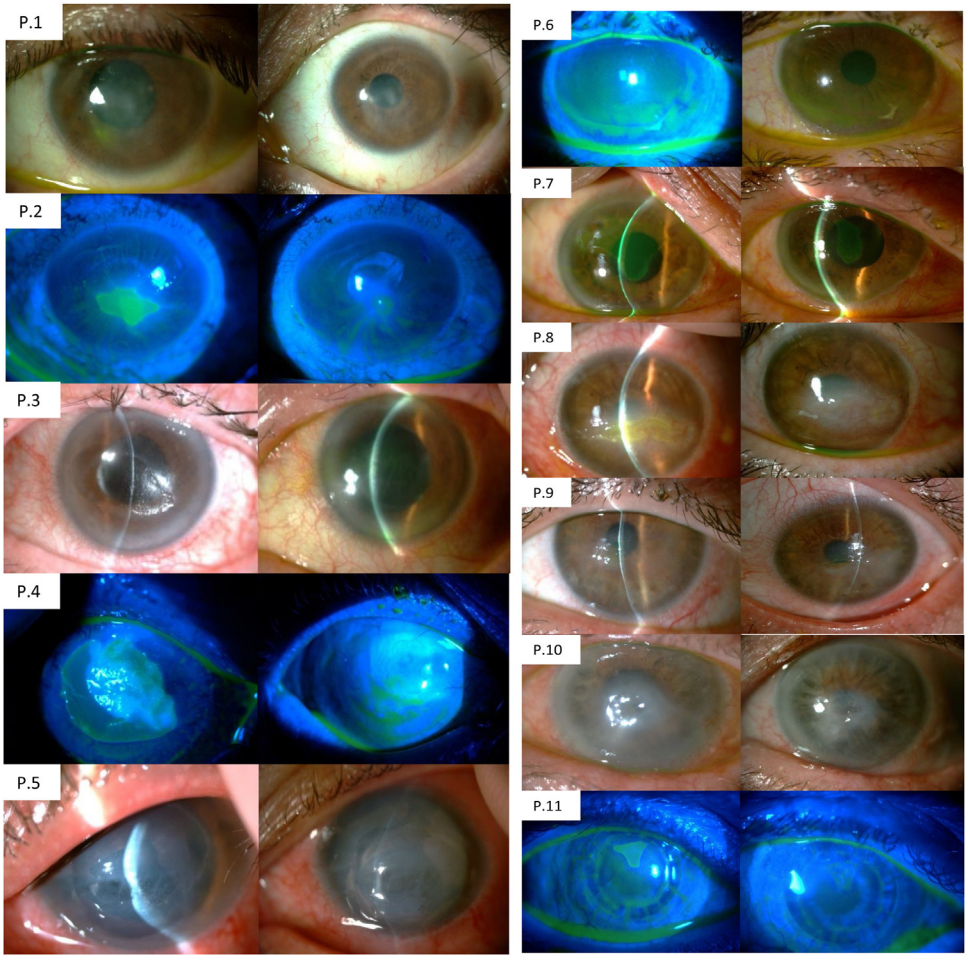

Fig. 1 – Corneal ulcers treated with Cacicol®. Left column: before treatment with Cacicol®. Right column: after treatment with Cacicol®, showing improvement or healing. Cases 5 and 9 failed, persistence of ulcer observed. Case 7 and 10 exhibit ulcer reduction and improvement.

73 and 100% of healing and VA improvements[3,8,14,18] other authors reported worse results and higher rates of failure with Cacicol® in patients with neurotrophic keratitis and no VA improvements.[15]

In what concerns time to healing, broad variability is observed which could be attributed to numerous factors including dosage, previous or co-adjuvant treatments, underlying cause of the disease, severity of the ulcer and patient comorbidities, to name a few. In what concerns posology, our team applied one drop every 2 days, and on average complete healing was reached 25 days after beginning treatment. Kymionis et al.[19] reported a healing time between 4 and 21 days with one daily drop of RGTA (Cacicol®, Laboratoires Thea, OTR3, París, France) and the fastest response was in a PED after cataract surgery without comorbidities. Aifa et al.[3] reported a mean of 8.7 weeks until healing, with one corneal ulcer of the 11 cases cured in a week. The applied dosage was similar to that of our protocol, i.e., one drop every 2 days. Chebbi et al.[7] applied RGTA OTR4120 on ulcers with severe corneal dystrophy in a dose of one drop per week during one month. Healing occurred in the third month.

Some authors modified dosages during the study. Guerra et al.[8] began treatment with one drop of Cacicol® per week but increased it to 2 in the absence of improvement, observing healing at week 4. Chappelet et al.[14] applied one drop of Cacicol® every 2 days during the first week as every 3 days during the following few weeks, with healing time being between 3 days and 3 months. Cochener et al.[13] utilized one drop of Cacicol® every 3 days during 2 weeks and subsequently the dose was maintained or adjusted to one weekly drop or every 2 days according to the evolution of each ulcer. The healing time was between one and 3 months. Other authors observed complete healing at 3 weeks after applying one drop every 2 days[5,20] and others utilized one drop twice a week.[21]

The reason why some authors tend to extend the time between instillations is because it is believed that an excess of RGTA could compete with growth factors and local cytokins which are also necessary to facilitate adequate healing processes. Some authors pointed out that the best dose could be one drop every 2 or 3 days.[3,22] However, another author utilized drops on a daily basis with excellent results.[19] The fact is that at this point in time posology continues to be based on the criterion of the ophthalmologist.

In the present case series, the range of days to healing was from 10 to 60 after beginning treatment with Cacicol®. This variability means that the healing of the ulcer could be attributed not only to the use of Cacicol® but to the concomitant treatment that was applied and to natural cell repair. However, we have observed 3 patients (cases 1, 2 and 11) who had 21 and 91 days of conventional therapy without improvement and there also was healed 10 days after the introduction of Cacicol® and case 6, after 67 days of unsuccessful conventional therapy had the answer resolved 30 days after beginning treatment with Cacicol®. This notable improvement attributable to Cacicol® is not found in all healed cases, and the following cases were treated longer with Cacicol® before achieving healing compared to the time during which they were in conventional treatment. For instance, case 4 (infected ulcer) receives 25 days of conventional therapy and was healed after receiving 3 cycles of Cacicol® during 45 days. Cases 7 and 10, who had received 17 and 7 days of conventional therapy, were cured after 60 and 18 days, respectively. This could be due to the difficulty involved in ulcer closure due to the addition of corticoids 2 core adjuvants treatment, to the medical criterion of giving a short period of time for conventional therapy and initiating therapy with Cacicol® at an early (albeit not immediate) stage, or to the old age of patients.

In what concerns the number of cycles, 6 out of 9 healed patients received one cycle of Cacicol® and 3 utilize between 2 and 3 cycles thereof. Between the first and second cycle of Cacicol® an interval of between 0 and 14 days was maintained. The authors believe that the interval between cycles, which was determined by the treating ophthalmologist, could have influenced the healing time. The literature does not provide uniformity in posology, timelines and other practical aspects of the use of Cacicol®. Some authors have reported continuous use of Cacicol® up to healing[13,15] while others utilized it for one month[14] and yet others extended it for a long time after healing.[5]

Out of the 2 failed cases, case 5 with keratocone and hydrops presented infectious keratitis by Acanthamoeba and filamentous fungi and received 4 cycles of Cacicol® exhibiting improvement after the first 2. However, the evolution of this patient was complicated by phacolytic glaucoma and finally failed, subsequently undergoing penetrating keratoplasty combined with phacoemulsification. Case 9 was a patient with systemic immunosuppression that received 2 cycles of Cacicol®. After the first one some improvement was observed but during evolution the ulcer worsened, and after 15 days the second cycle was initiated without success. In both cases it appears that Cacicol® had an initial positive effect, and this could have delayed the immediate application of subsequent cycles of Cacicol®. In addition, the severity of the condition and the complexity of patients probably contributed to worsen prognosis and for this reason success was not achieved.

A further factor that could influence the healing time with Cacicol® is the toxicity of utilized drugs, such as antibiotics or antivirals. Arvola et al.[15] mentioned that 3 of the 4 failed cases were treated with fluoroquinolones which can inhibit epithelial growth due to positive regulation of ECM metalloproteinases.[23]

Co-adjuvant treatments comprised mainly preservative-free artificial tears that can be applied on their own[5] or with cyclosporine,[3] therapeutic contact lenses,[19] topical antibiotics of corticoids,[14] vitamin A cream, topical antivirals,[13,15] and/or doxycycline.[20] The present case series included patients with a range of adjuvant treatment according to their underlying pathology, including artificial tears with hyaluronic acid without preservatives, 20% autologous serum, erythromycin cream, antibiotic eye drops with quinolone and tobramycin, voriconazole, chlorhexidine, propamidine and atropin (Table 1).

In conventional corneal ulcer treatment, autologous serum is frequently used although it has the disadvantage of needing a blood sample of the patient with the risk of contamination and safety of health professionals.[3,24] In the present case series, autologous serum was utilized in 82% of cases, in con-

trast with Arvola et al.[15] who utilized this product only in one patient and other authors who did not utilize it at all.[3,5,13,20] Possibly, the joint use of Cacicol®, autologous serum and therapeutic contact lenses[19] is a good combination for treating neurotrophic corneal ulcers. In addition, Cacicol® is a safe product for patients as well as health professional since it is easy to store, is available in pharmacies and has demonstrated effectiveness. The main drawback of Cacicol® is its high cost, particularly in Spain where it is not covered by the national health system and the full economic burden is on the patient's shoulders. At present, the distribution of this product in Spain has been halted due to industrialization reasons as reported by a press release of Laboratorios Thea and OTR3 in December 2019.[25]

There are very few publications on the use of Cacicol® for corneal overinfections of neurotrophic ulcers.[5,14] Mateo et al.[5] reported one corneal ulcer infected by Acanthamoeba and treated with Cacicol® together with preservative-free artificial tears during 8 weeks with successful results.[5] Chappellet et al.[14] reported 100% healing of patients with residual PED after treatment of an infected corneal ulcer. We reported 2 infected cases (4 and 5) and initiated treatment with Cacicol® at an early stage in 2 risk patients who exhibited previous history of corneal ulcer with poor evolution in order to avoid additional severe complications such as melting, corneal scarring or perforation.

The main limitations of the present study are those inherent to retrospective studies such as the loss of data or non-systematic collection, co-adjuvant use with other therapies simultaneously with Cacicol® treatment (intervention bias), measurements carried out by different observers that could have produced an information bias as well as the heterogeneity of cases included in the study with a range of etiologies and treatments.

Additional studies are necessary to explore the possible benefits of Cacicol® in several indications including infected corneal ulcers to establish posology, explore the efficacy of repeated cycles and intervals between them in order to define an improved treatment algorithm.

Cacicol® seems to be a promising option for treating corneal ulcers with torpid evolution or poor response to conventional treatment. Early use in selected cases and successful treatment cycles seems to be useful.

Funding

This research has not received specific support from agencies of the public or private sector, or from nonprofit entities.

Conflict of interest

No conflict of interests was declared by the authors.

Acknowledgments

The authors wish to acknowledge the entire team of the Ophthalmology Dept. of the San Carlos Clinic Hospital of Madrid, Spain, who attended to the patients included in this study and participated in research.

REFERENCES

1. Lambiase A, Rama P, Aloe L. Management neurotrophic keratopathy. Curr Opin Ophthalmol. 1999;10:270–6.
2. Davis EA, Dohlman CH. Neurotrophic keratitis. Int Ophthalmol Clin. 2001;41:1–11.
3. Aifa A, Gueudry J, Portmann A, Delcampe A, Murraineet M. Topical treatment with a new matrix therapy agent (RGTA) for the treatment of corneal neurotrophic ulcers. Invest Ophthalmol Vis Sci. 2012;53:8181–5.
4. Alcalde I, Íñigo-Portugués A, Carreño N, Riestra AC, Merayo-Lloves JM. Effects of new biomimetic regenerating agents on corneal wound healing in an experimental model of post-surgical corneal ulcers. Arch Soc Esp Oftalmol. 2015;90:467–74.
5. Mateo A, Abadia B, Calvo P, Minguez E, Pablo L, Del Castillo JM. Treatment Of Acanthamoeba neurotrophic corneal ulcer With topical matrix therapy. J Ophthalmic Inflamm Infect. 2015;5:18.
6. Semeraro F, Forbice E, Romano V, Angi M, Romano M, Filippelli RM, et al. Neurotrophic keratitis. Ophthalmologica. 2014;231:191–7.
7. 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.
8. Guerra M, Marques S, Quadrado Gil J, Campos J, Ramos P, Rosa AM, et al. Neurotrophic keratopathy: therapeutic approach using a novel matrix regenerating agent. J Ocular Pharmacol Therap. 2017;33:662–9.
9. Aslanides IM, Selimis VD, Bessis ND, Georgoudis PN. A pharmacological modification of pain and epithelial healing in contemporary transepithelial all-surface laser ablation (ASLA). Clin Ophthalmol. 2015;9:685–90.
10. Xeroudaki M, Peebo B, Germundsson J, Fagerholm P, Lagali N. RGTA in corneal wound healing after transepithelial laser ablation in a rabbit model: a randomized, blinded, placebo-controlled study. Acta Ophthalmol. 2016;94:685–91.
11. 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;29:457–78.
12. Kymionis GD, Liakopoulos DA, Grentzelos MA, Tsoulnaras KI, Detorakis ET, Cochener B, et al. Effect of the regenerative agent poly (Carboxymethylglucose Sulfate) on corneal wound healing after corneal cross-linking for keratoconus. Cornea. 2015;34:928–31.
13. Cochener B, Zagnoli C, Hugny-Larroque C, Derrien S. Healing resistant corneal ulcers neurotrophic using a matrix regenerating agent. J Fr Ophtalmol. 2018;42:159–65.
14. Chappelet MA, Bernheim D, Chiquet C, Aptel F. Effect of a new matrix therapy agent in persistent epithelial defects after bacterial keratitis treated with topical fortified antibiotics. Cornea. 2017;36:1061–8.
15. Arvola RP, Robciuc A, Holopainen JM. Matrix regeneration therapy: a case series of corneal neurotrophic ulcers. Cornea. 2013;35:451–5.
16. Bonini S, Rama P, Olzi D, Lambiase A. Neurotrophic keratitis. Eye (Lond). 2003;17:989–95.
17. Versura P, Giannaccare G, Pellegrini M, Sebastiani S, Campos E. Neurotrophic keratitis: current challenges and future prospects. Eye and Brain. 2018;10:37–45.

18. Timaru C-M, Stefan C, Iliescu DA, De Simone A, Batras M. Matrix regenerative therapy. Rom J Ophthalmol. 2017;61:2–10.
19. Kymionis GD, Liakopoulos DA, Grentzelos MA, Diakonis VF, Klados NE, Tsoulnaras KI, et al. Combined degenerative topical application of a regenerative agent with a bandage contact lens for the treatment of persistent epithelial defects. Cornea. 2014;33:868–72.
20. Ustaoglu M, Solmaz N, Onder F. Ocular surface chemical injury treated by regenerating agent (RGTA Cacicol20). GMS Ophthalmol Cases. 2017;7. Doc28.
21. De Monchy I, Labbe A, Pogorzalek N, Gendron G, M'Garrech M, Kaswin G, et al. Management of herpes zoster neurotropic ulcer Using a new matrix therapy agent (RGTA): a case report. J Fr Ophtalmol. 2012;35:187, e1-6.
22. Sacchetti M, Lambiase A. Diagnosis and management of neutrotrophic keratitis. Clin Ophthalmol. 2014;8:571–9.
23. Reviglio VE, Hakim MA, Song JK, O'Brien TP. Effect of topical fluoroquinolones on the expression of matrix metalloproteinases in the cornea. MBC Ophthalmol. 2003;3:10.
24. Geremicca W, Fonte C, Vecchio S. Blood components for topical use in tissue regeneration: evaluation of corneal lesions treated with platelet lysate and considerations on repair mechanisms. Blood Transfus. 2010;8:107–12.
25. Laboratorios Thea y OTR3. Retirada del Cacicol. https://www.facoelche.com/noticias/retirada-del-cacicol/; 2019 [accessed 3 Apr 2020].