Title: Use of nicergoline as adjunctive treatment of neurotrophic keratitis in routine clinical practice: a case series.

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Abstract:

Purpose: To describe the effectiveness and safety of nicergoline in patients with epithelial corneal defect or corneal ulcer due to neurotrophic keratitis.

Methods: A prospective case series review was performed in 14 patients (14 eyes) with neurotrophic keratopathy who started treatment with nicergoline as an off-label prescription from January to November of 2020. Patients with a epithelial defect or corneal ulcer due to neurotrophic keratitis were treated with 10 mg of oral nicergoline twice daily.

Results/Serial cases: Complete corneal healing was observed in 10 (71.4%) of the 14 patients after 25.6 ± 26.60 days (range 7-90) with nicergoline. In three (21.5%) patients the wound healing was not achieved (all of them with autoimmune disease), and one patient (7.1%) was lost to follow-up. Eleven patients (79%) were females; the average age at consultation was 69 years (44-96). The mean time between diagnosis and the starting of nicergoline was 10.92 ± 8.85 days (0-28). No adverse effects of nicergoline were observed in any subject.

Conclusion: Nicergoline as an adjunctive treatment for neurotrophic keratitis showed a potential use in the healing of epithelial defect with a good tolerance in real-life clinical practice.

Introduction:

The cornea is the most densely innervated tissue in the body. Corneal innervation plays an important role in the maintenance and proliferation of the corneal epithelium, and therefore, in wound healing.[1] A partial or total loss of corneal sensitivity leads to the development of neurotrophic keratitis (NK).[1] NK is a rare degenerative entity which prevalence has been estimated at approximately 1.6-4.2 / 10,000.[2] However, recently has been suggested that NK may be more frequent than previously reported.[2] A wide range of ocular or systemic conditions can cause NK, including chronic use of topical drugs (such as glaucoma medications, anaesthetics and/or nonsteroidal anti-inflammatory drugs), ocular surgery, severe dry eye disease, diabetes, neurosurgical procedures, and the most frequent condition, herpetic keratitis. All of them are characterized by corneal hypoesthesia or anaesthesia.[3]

Untreated NK leads to a decrease in visual acuity and can lead to severe complications putting ocular integrity at risk. Therefore, it is suggested that NK-specific treatment should be initiated as soon as the diagnosis is suspected.[4] NK requires a specific therapeutic approach depending on the degree of severity and the evolution over time. Although almost all current therapies aim to promote wound healing and prevent injury progression, they are not able to actively stimulate nerve regeneration.[1]

Nicergoline, (Sermion® [Biogenesis AntiAging, Fish Hock, South Africa]), is an ergot alkaloid derivative clinically available from the 1970s. Nicergoline has neurotrophic and antioxidant properties; it is widely used in the treatment of cognitive impairment secondary to ischemic stroke and other degenerative dementias, migraine or, dizziness.[5] Nicergoline has been reported to accelerate wound healing in rat corneas.[6] Likewise, recently a prospective study demonstrated with the off-label use of nicergoline a wound healing rate of 85% in patients with NK refractory to conventional therapy.[7] In this series of cases, our aim is to describe the effectiveness and safety of the off-label use of

nicergoline in patients with NK in real-life clinical practice, reinforcing previous outcomes.[7]

Methods:

A prospective review was performed of serial cases of patients with NK who started treatment with nicergoline as an off-label prescription at a single tertiary centre from January to November of 2020. The Mackie's classification was used to assess the NK stage: stage 2 (persistent epithelial defect of more than 14 days without stromal involvement) or 3 (corneal ulcer) according to Mackie's classification.[4] The patients received oral nicergoline in 10mg doses twice daily; previous and concomitant treatment were variable according to medical criteria. The association of nicergoline with conventional treatment, as well as the duration of the treatment and the frequency of follow-up consultations, were decided according to individualized medical criteria depending on the clinical evolution of each patient. A comprehensive medical and ophthalmic history was elicited in each patient.

Diagnosis was based on slit-lamp examination and fluorescein staining. Complete healing was defined as negative corneal fluorescein staining. Treatment outcome was considered successful if total corneal epithelial healing was achieved without requiring further additional interventions after initiation of nicergoline. Healing of the epithelial corneal defect was assessed by fluorescein staining and measurement by slit lamp. Impairment of corneal sensitivity was assessed at the initial diagnosis of NK with a cotton tip, but was not evaluated during treatment with nicergoline. Adverse events were checked by anamnesis in every follow-up visit. The diagnosis of microbial keratitis was excluded by culture of the corneal sample took by a sterile swab.

The study protocol was reviewed and approved by the Ethics Committee of Clinic Hospital of Barcelona. The data collection was done in compliance with the Declaration of Helsinki (October 2013).

Results/case series:

Fourteen eyes of 14 patients were reviewed. No patient had a bilateral NK during treatment with nicergoline. Eleven patients (79%) were females and three were males. The average age at consultation was 69 years (range 44-96). Herpes virus infection (one herpes simplex and two varicella zoster) were the most frequent aetiology (21%) of NK.

The other causes of NK were: autoimmune condition in two patients, graft versus host disease (GVHD) in two patients, severe exophthalmos in a patient with active thyroid-associated orbitopathy, a patient with a history of lacrimal gland excision one year ago due to nodular fasciitis, a patient with toxic corneal epitheliopathy induced by topical treatment for severe glaucoma and in four patients during the postoperative period after corneal transplantation. Regarding patients with autoimmune disease, one had an ocular mucous membrane pemphigoid (treated with rituximab, mycophenolate and dapsone) and the other, severe dry eye disease secondary to a primary biliary cirrhosis in an advanced stage (the fellow eye had been eviscerated due to recurrent ocular perforations). Half of all patients had history of corneal transplantation (six penetrating keratoplasty and one Descemet Stripping Automated Endothelial Keratoplasty - DSAEK); three of them had received more than one graft. Three of the 14 patients were also diabetic.

The mean time between diagnosis and the starting of nicergoline was 10.92 ± 8.85 days (0-28). In two cases (cases 1 and 8), nicergoline was started at the time of diagnosis of

the epithelial defect according to the Ophthalmologist criteria due to previous success in epithelial healing in other patients. These two cases were diagnosed as NK in Mackie's stage 3 (stromal involvement, with associated epithelial defect) due to clinical characterised. The average of the largest diameter of epithelial defect at diagnosis was 4.0mm (0.5-9.0). Regarding the location of the epithelial defect, it was central in nine (64%) cases. The Mackie's classification stage at diagnosis was stage 2 in three patients and stage 3 in nine patients. Two patients (cases 4 and 14) presented NK with an epithelial defect but with a duration of epithelial defect of less than 14 days at the time of initiation of nicergoline. In both cases, the margins of the defect were rolled and in case 4 there were also Descemet's folds. Both clinical features (rolled margins and Descemet folds) are typical of NK. The baseline best corrected visual acuity (BCVA) for eight (57%) eyes was counting fingers or less. All patients were on artificial tears containing sodium hyaluronate, 79% were on topical antibiotics and 29% on oral antivirals prior to the initiation of nicergoline.

Complete corneal healing was observed in 10 (71.4%) of the 14 patients after 25.6 ± 26.60 days (range 7-90) with nicergoline. In three (21.5%) patients the wound healing was not achieved (in case 9, the defect finally healed, but required amniotic membrane transplantation (AMT) therefore, a favourable outcome with nicergoline is not completely considered), In one patient (7.1%) there was a loss to follow-up, although a 50% reduction in the size of the epithelial defect was observed in the first visit after starting nicergoline. Corneal wounds healed one week after starting nicergoline in three eyes, between the first and second week in three eyes, in two patients wound healing was observed at 30 days and two eyes required more than one month (60 and 90 days, respectively). The mean epithelial defect duration was 10.92 ± 8.85 days (ranged from 0 to 28 days) and the treatment success duration was 25.63 ± 26.60 days (ranged from 7 to

90 days). Epithelial defect was separated within less than one week and more than one week. In less than one-week epithelial defect duration (2.83 ± 2.63 days) treatment success duration was 23.60 ± 22.41 days and in more than one-week epithelial defect duration (17.00 ± 6.50 days) treatment success duration was 27.33 ± 31.72 days (P = 0.83)

During follow-up, we observed one case of recurrence after the total wound healing while nicergoline was ongoing. In this case, the treatment with nicergoline was maintained as well as the topical antibiotic and immunomodulator, and a therapeutic contact lens was placed. The epithelial defect healed successfully again after 10 days. . The mean duration of nicergoline treatment (taking into account all patients except the one with loss of follow-up) was 33 days (13-90). No adverse effects (AE) of nicergoline were observed in any subject.

Overall, 3 (21%) patients required surgical procedures during treatment with nicergoline due to decompensation from their underlying disease: tectonic lamellar keratoplasty, AMT and symblepharon ring implant to treat an ocular perforation (26 days after starting nicergoline) in the patient who suffered mucous membrane pemphigoid, and amniotic membrane implantation because of persistence of epithelial defect in two patients (cases 5 and 9).

The baseline characteristics and clinical evolution after starting nicergoline are summarized in Table 1 and Table 2, respectively. Figures 1 and 2 show healing of a neurotrophic epithelial corneal defect before and after treatment with nicergoline.

Discussion:

Treatment of epithelial defect associated to NK remains as a challenging management in routine clinical practice. Adjunctive treatment with oral nicergoline has shown to be effective and safe in our case series. Under normal conditions, corneal nerve fibers release neuromediators (such as substance P) that provide trophic support to the ocular surface and maintaining the anatomical integrity. At the same time, epithelial cells release growth factors such as nerve growth factor (NGF) that stimulate the differentiation and maturation of the corneal nerve fibers and epithelial cells.[8] NK etiopathology leads to spontaneous epithelial breakdown and corneal ulceration. The management of this condition currently is a challenge due to the lack of pathophysiology treatments targeting nerve regeneration.

To overcome this limitation, the use of neuropeptides and NGF for the treatment of NK is being evaluated in several promising studies. It has been observed in various studies that the combination of substance P and insulin-like growth factor-1 induces a synergistic effect; as an example, in 26 eyes with NK-associated persistent epithelial defect, the epithelial defects resurfaced completely in 73% of the cases within 4 weeks after treatment.[9] Recently, the NGF0214 trial evaluated the use of topical recombinant human NGF. At 8 weeks, 69.6% of NGF-treated patients achieved <0.5mm staining lesion vs 29.2% vehicle-treated patients.[10] Similar results were obtained in the REPARO phase II study.[11] The use of topical insulin in refractory epithelial defect has also been successfully evaluated.[12] In this group of therapies targeting the pathogenic mechanisms of NK, nicergoline may play an important role.

In vivo studies demonstrated that nicergoline has a protective effect on the degeneration of cholinergic neurons induced by NGF deprivation in the brain of aged rats.[13] Based on these findings, the effect of nicergoline on corneal tissue has been evaluated.

Nicergoline has been shown to accelerate corneal wound healing in rats by increasing NGF levels in the lacrimal gland and in the cornea.[6]

Recently, a prospective study evaluated nicergoline treatment in 27 eyes of 24 patients with NK unresponsive to conventional therapy. In 23 eyes (85%) the defects healed completely between 7 and 30 days of treatment.[7] Based on these findings; they postulate that nicergoline facilitates the healing of epithelial defects. Similar results in the efficacy of nicergoline are observed in our case series: 71.4% of the epithelial defects resurfaced after treatment with nicergoline, reinforcing this previous study[7] outcomes of the possible effectiveness of the nicergoline as adjunctive treatment for corneal epithelial healing. The period of time between the start of nicergoline and the complete healing is highly variable (7-90 days) in our case series which is quite different from this study.[7] This fact could be due to the variety and complexity of the aetiologies shown by some of our patients (autoimmune diseases, GVHD, thyroid-associated orbitopathy, lacrimal gland excision, etc). In our research, we found a difference of 4 days in treatment success duration within less than one-week epithelial defect duration (23.60 ± 22.41 days) and more than one-week epithelial defect duration (27.33 ± 31.72 days), P= 0.83. These results were clinically but not statistically significant probably due the relatively small sample caused by the rare condition analysed. Three patients required surgical procedures after starting nicergoline (cases 2, 5 and 9) and eventually only one of them achieved the epithelial defect closure after AMT (which was done twelve days after starting nicergoline). There was one case of recurrence of the epithelial defect during treatment with nicergoline, but it healed after ten days while the treatment with nicergoline was maintained. In the prospective study of 24 patients treated with nicergoline, diabetes mellitus was the cause of NK in more than half of the patients (15/24) and in most of the rest of the patients the cause was after neurosurgery

or retinal surgery; no patient had undergone corneal transplant surgery.[7] Therefore, we hypothesized that although our cases could be more complex due to their underlying pathology, the nicergoline supplement was effective in most of them. Actually, corneal transplantation had been performed in half of our patients, 5 of them in the last three months. Corneal transplantation in NK has a worse prognosis due to the persistent risk of developing epithelial defects, ulcers, and corneal melting after surgery.[4] According to the Mackie's classification, nine patients (64%) had stage 3 disease, compared to 44.4% of the cases in the mentioned study. In this study, nicergoline was started after at least two months of lack of response to conventional treatment.[7] In our case series, the time of initiation of nicergoline depended on the judgment of the physician. In two cases (cases 1 and 8) nicergoline was started at the same time as the diagnosis of the epithelial defect (associated with stromal involvement), with good outcome in both cases. The patient in case number 1 was treated with artificial tears and nicergoline from the diagnosis of the epithelial defect on the neurotrophic ulcer. She was an elderly patient (92 years old) who had difficulty coming to the medical consultation. The next time the patient was able to come to the visit was 30 days after starting nicergoline and the defect was found to be healed. The patient in case 8 had a corneal ulcer with an epithelial defect, topical antibiotic treatment was started at the same time as nicergoline when the epithelial defect was observed. Neither case was previously treated by other providers.

Nicergoline is a drug widely used for several years for other diseases, especially neurological, and its safety is well known. Its AE are generally mild and transient. Nausea, dry mouth, headache and hot flushes have been described, but discontinuation of treatment due to AEs is infrequent.[5] No nicergoline-related AEs were observed in any of our patients, as well as in the previously cited study.[7]

Some limitations of this study have to be disclosed: in our case series the change in corneal sensitivity and NGF levels were not recorded postoperative, unlike in the prospective study.[7] The change in BCVA with nicergoline has not been evaluated either, because the baseline BCVA of our patients was very low and the initial visual prognosis was poor in many of them. However, our main objective was to evaluate the healing of the epithelial defect. Other limitation of our case series is the lack of a group of control cases, and one of the most important problems of the study is that the patient population was highly heterogeneous. Presence of adverse events were asked at every follow-up visit. However, a standardized questionnaire to check them could reveal mild adverse events ignored by the patients.

To our knowledge, this is the second report about the off-label use of nicergoline for the treatment of corneal epithelial defects, and the first case series of patients on this therapy in real-life clinical practice with a variety of complex cases. In conclusion, nicergoline may show a potential use in the healing of epithelial defects with a good tolerance in real-life clinical practice, both in refractory cases and as adjunctive treatment after the diagnosis of the epithelial defect in NK. Confirmation of its therapeutic efficacy will require randomized control studies with a larger number of patients.

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FIGURE CAPTIONS:

FIGURE 1: Case 7. Patient with absence of corneal sensitivity secondary to neurotrophic keratopathy due to herpes simplex virus. One month after penetrating keratoplasty with amniotic membrane transplantation, a epithelial defect developed at the host-receptor interface. (A and B) Persistent epithelial defect after 14 days of treatment with oral valaciclovir and topical ofloxacin, before starting nicergoline. (C and D) The epithelial defect healed after 13 days of nicergoline treatment.

FIGURE 2: Case 11. Neurotrophic keratopathy in a patient with ocular graft versus host disease and penetrating keratoplasty 5 years earlier. (A and B) Corneal ulcer on treatment with oral doxycycline and topical moxifloxacin for 7 days without improvement, before starting nicergoline. (C and D) The corneal ulcer healed after 14 days of nicergoline treatment. Case 3. A 71-year-old patient presented with a corneal ulcer in the context of rejection after penetrating keratoplasty. (E) The corneal ulcer covers practically the entire diameter of the graft despite eight days of treatment with no signs of improvement before starting nicergoline. (F)

One week after starting nicergoline, a 50% decrease in the size of the ulcer was observed.

Table 1. Summary of baseline characteristics.

Case	Age/ Sex	Affected Eye	Underlying Condition	BCVA (Decimal)	Mackie Classification Stage	Wound Location	Largest Diameter of Epithelial Corneal Defect (mm)
1	92/F	R	Toxic corneal epitheliopathy/Diabetes	0,05	3	Central	2
2	77/F	L	Ocular pemphigoid	CF	3	Inferior	5
3	71/F	R	Graft rejection after PK	0,1	3	Central	6
4	73/F	R	Postoperative of PK	CF	*	Central	4
5	49/F	R	Primary biliary cirrhosis/Postoperative of PK	CF	3 (corneal melting)	Central	6,5
6	78/M	L	Lacrimal gland excision	CF	3	Nasal	2,5
7	72/F	L	Herpes simplex keratitis/PK Postoperative	HM	2	Inferior	Interface host-donor (IV–VIII hours)
8	51/F	L	PK Postoperative	HM	3	Central	2,5
9	70/F	L	Severe thyroid-associated orbitopathy	LP	3	Central	9
10	73/F	L	Ocular GVHD (recurrent corneal melting in the other eye)	0.16	2	Central	3,5
11	56/F	L	Ocular GVHD (PK 5 years ago)	CF	3 (corneal melting)	Central	3
12	71/M	R	DSAEK postoperative/Diabetes	0,2	3	Central	6
13	96/F	L	Herpes zoster keratitis	0,1	2	Inferior	0,5
14	44/M	L	Herpes zoster keratitis/Diabetes	0,5	*	Temporal	2

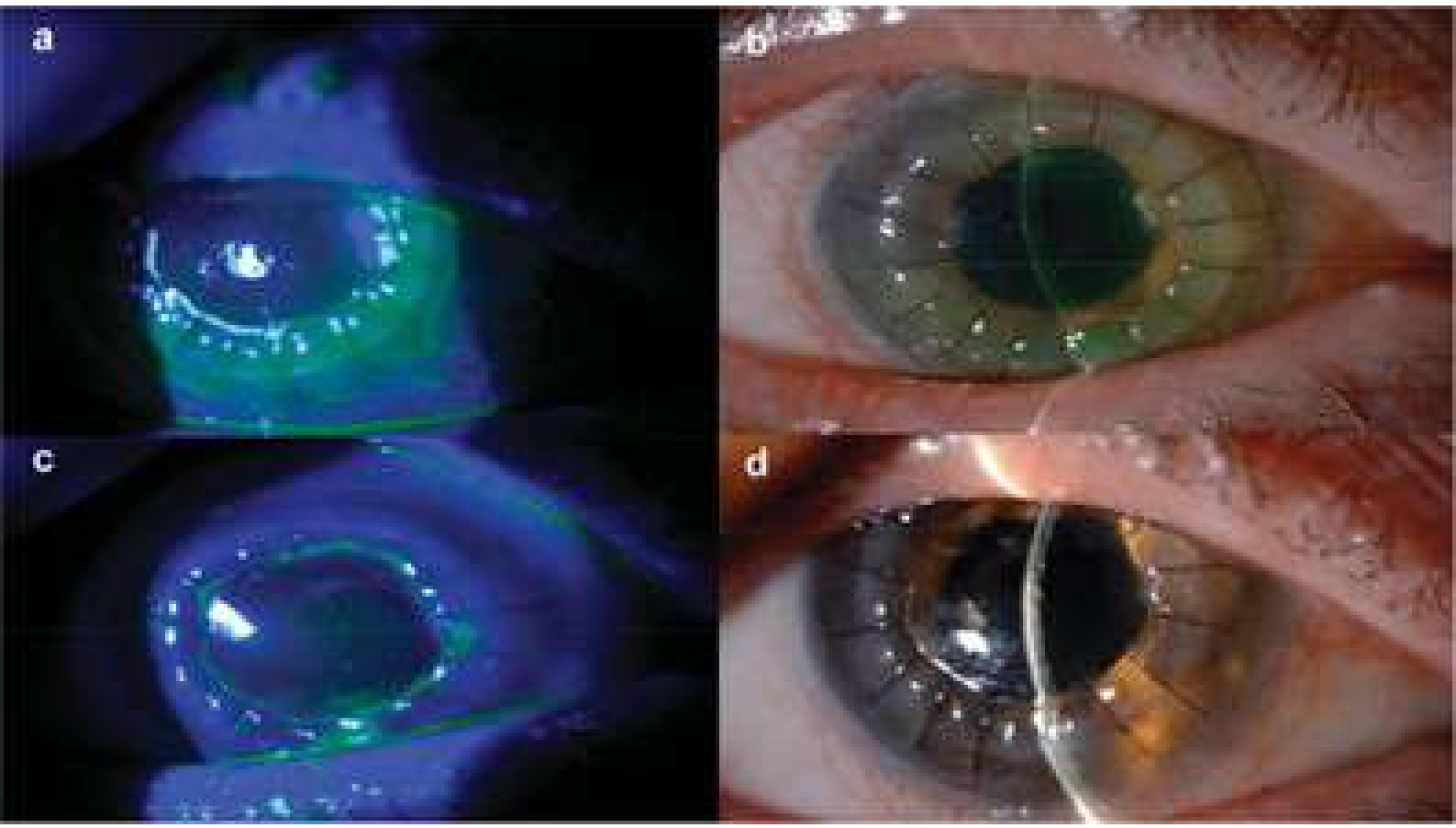
*: Patient with neurotrophic keratitis without stromal involvement, and an epithelial defect of less than 14 days.

BCVA: best corrected visual acuity; F: female; M: male; R: right; L: left; PK: penetrating keratoplasty; GVHD: graft versus host disease; DSAEK: Descemet stripping with automated endothelial keratoplasty; CF: counting finger; HM: hand movement; LP: light perception.

Table 2. Summary of the clinical course of the patients.

Case	Previous Treatment (excluding artificial tears)	Time between Diagnosis and Nicergoline (days)	Time to complete Healing from Nicergoline (days)	Days on nicergoline Treatment	Recurrence	Surgery
1	-	0	30	42	No	No
2	Oral valaciclovir, oral doxycycline, chloramphenicol, dexamethasone	14	-	25	-	Tectonic LK Symblepharon ring
3	Netilmicin, therapeutic soft contact lens	8	30	14	No	No
4	Ofloxacin	3	60	80	No	No
5	Ofloxacin, therapeutic soft contact lens	28	-	30	-	AMT
6	Vancomycin, ceftazidime	3	7	37	No	No
7	Oral valaciclovir, ofloxacin	14	13	13	No	No
8	Netilmicin, ofloxacin, therapeutic soft contact lens	0	7	14	No	No
9	Vancomycin, ceftazidime, doxycycline, amphotericin	24	14	14	No	AMT
10	Ofloxacin, doxycycline, ciclosporin, tacrolimus	14	10	40	Yes	No
11	Doxycycline, moxifloxacin	7	14	14	No	No
12	Ofloxacin, therapeutic soft contact lens	20	90	90	No	No
13	Oral valaciclovir	14	7	14	No	No
14	Oral valaciclovir	4	NA*	NA	NA	No

*: 50% reduction in the diameter of the defect in the first control, subsequently the follow-up was lost. NA: not available; LK: lamellar keratoplasty; AMT: amniotic membrane transplantation.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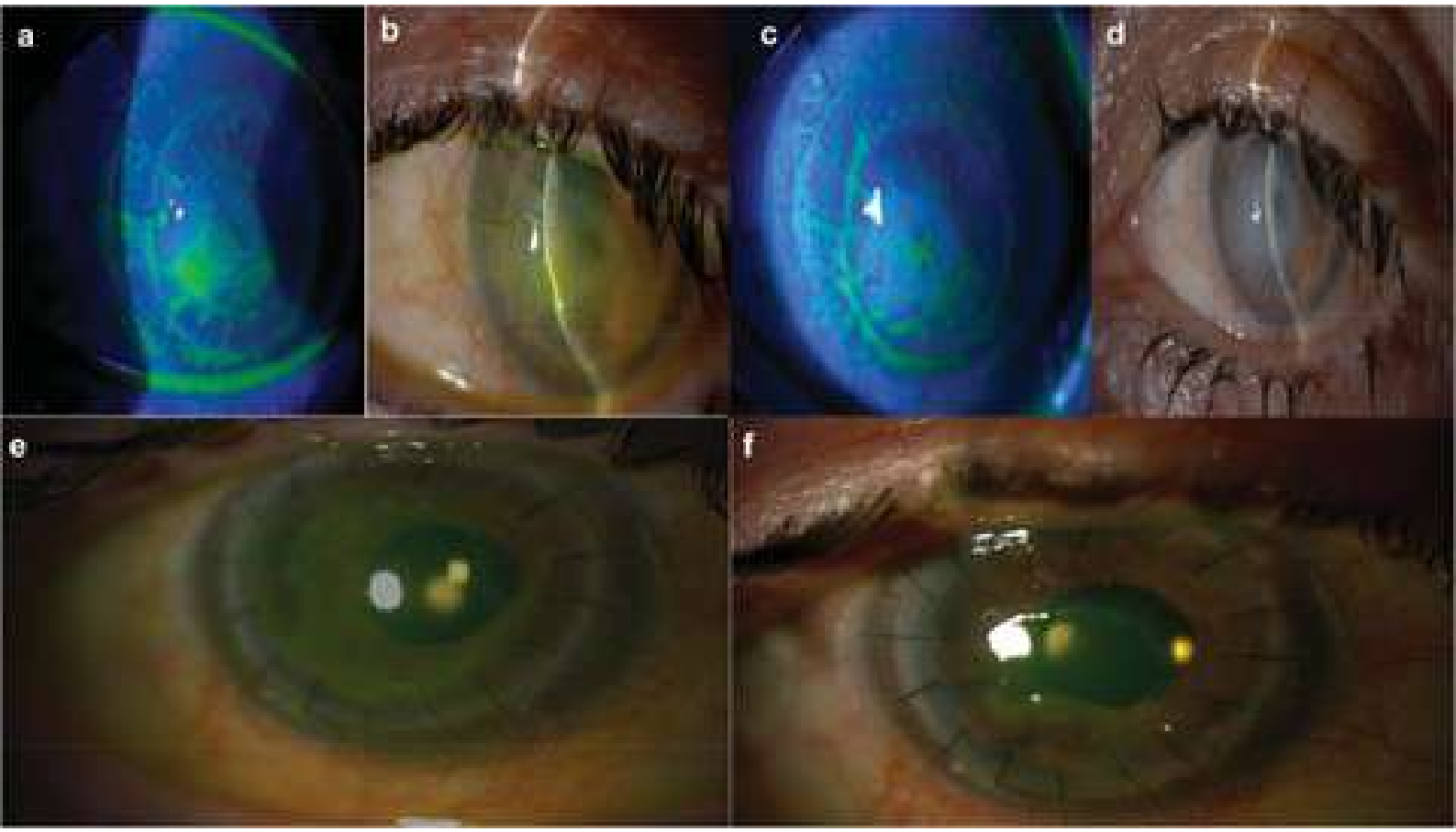
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