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Research Article

Ciclosporin 0.1% Cationic Emulsion Eye Drops in the Treatment for Iatrogenic Ocular Surface Disease in Glaucoma Patients: A Retrospective Case Series

Raheel Faiz [1], Nazanin Nosrati [1], Amun Sachdev [1], Rosemary Robinson [1], Ankur Barua [1], Ahmad Muneer Otri *[1]

1. Department of Ophthalmology, University Hospital, University Hospitals of Coventry and Warwickshire NHS Trust, UK.

***Correspondence to:** Ahmad Muneer Otri, Department of Ophthalmology, University Hospital, University Hospitals of Coventry and Warwickshire NHS Trust, UK.

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Abstract

Background/objectives: *Ciclosporin 0.1% cationic emulsion eye drops have been approved by the European Medicines Agency for the treatment of severe ocular surface disease (OSD) related to dry eyes. The current study aimed to assess the therapeutic effect of ciclosporin 0.1% eye drops in the treatment of OSD secondary to chronic topical anti-glaucoma therapy among patients who had failed to respond to conventional dry eye treatments.*

Methods: *A retrospective, observational case series was conducted concerning 8 patients (14 eyes) with OSD secondary to chronic anti-glaucoma drop use who had attended specialist glaucoma clinics at the University Hospital of Coventry and Warwickshire. Ocular surface symptoms and signs were examined for patients who had received topical ciclosporin 0.1% cationic emulsion treatment (one drop, once daily) for a minimum follow-up period of 6 months, with outcomes compared against baseline (pre-ciclosporin).*

Results: *All but one patient included in the review (87.5%) reported symptomatic improvement following treatment with ciclosporin 0.1% eye drops. This corresponded with a clinical improvement in ocular surface signs. Half of all eyes had an improvement in visual acuity. One patient discontinued treatment after 3 months due to intolerance and worsening of ocular surface disease symptoms. There were no clear adverse effects on intraocular pressure.*

Conclusions: *Topical ciclosporin 0.1% cationic emulsion may be considered in the treatment of iatrogenic dry eyes and ocular surface disease in glaucoma patients who have failed to respond to conventional treatments, in particular, when there is a concern with topical steroids and a rise in intraocular pressure.*

Key words: *Ocular surface disease, Ciclosporin 0.1%, Glaucoma, Dry eye, Iatrogeni*

Introduction

Dry eye-related ocular surface disease (OSD) is a common condition with a prevalence of up to 35% in certain populations [1]. The condition is multifactorial and is characterised by a vicious cycle of tear-film instability leading to tear hyperosmolarity, epithelial damage and surface inflammation with overall disruption of the lacrimal functional unit [2,3]. Breakdown of the ocular surface gives rise to symptoms of discomfort, foreign body sensation, photophobia, fluctuating visual acuity (VA) and fatigue [2–4]. The prevalence of OSD is affected by increasing age, female sex, dry environments, impaired blinking, presence of meibomian gland dysfunction (MGD) and blepharitis and chronic use of topical medication, especially preservative-containing eye drops [5–7].

Benzalkonium chloride (BAK) is a commonly used preservative in eye drops, particularly within anti-glaucoma medications, and is known to be harmful to the ocular surface. It initiates the cycle of OSD by destabilising the pre-corneal tear film due to its detergent effect on the lipid layer and decreases the density of the conjunctival epithelium goblet cells required for mucin secretion; from this, epithelial damage and surface inflammation ensues [5,8,9].

Patients requiring anti-glaucoma drops for intraocular pressure (IOP) control often need to use such topical therapies regularly for extended durations, sometimes indefinitely [10]. Furthermore, the majority will require double or even triple medical therapy for adequate pressure control [10]. Inevitability, this causes a cumulative toxicity to the ocular surface [2,5,10–14].

Previous epidemiological studies have shown that, amongst the side-effects that can be caused by anti-glaucoma drops, eye irritation is a common complaint [13,15,16]. On clinical examination, the most commonly reported signs include conjunctival injection, decreased function and production of tears and punctate epithelial erosions (PEEs) [17]. These findings have been supported by in vivo confocal microscopy studies which have demonstrated changes to the ocular surface and tear function among patients on long-term anti-glaucoma drops [18]. Squamous cell metaplasia, the presence of inflammatory markers and decreased sub-basal nerve fibre distribution, also contribute to the onset of OSD in such patients [17,19]. Interestingly, these changes have been shown to persist even after stopping anti-glaucoma drops [5,20]. With that in mind, OSD secondary to glaucoma treatment is a highly prevalent condition. The troublesome symptoms of OSD can have negative impacts on a patient's quality of life and even deter adherence with therapy [2,12,14].

Current management of OSD secondary to glaucoma drops includes changing to preservative-free (PF) drops, using ocular lubricants, short-term topical steroids, management of MGD, punctal plugs or using alternative methods of IOP control such as selective laser trabeculoplasty (SLT) or surgical options [2,17]. However, these alternatives may have an adverse or sub-optimal effect upon IOP, be ineffective in addressing the underlying inflammatory element of the OSD long-term or be associated with other complications related to laser or surgery. Therefore, more targeted approaches are essential for the management of glaucoma patients with iatrogenic OSD.

Ciclosporin is an immunomodulatory and anti-inflammatory agent [21]. Ciclosporin 0.1% (1mg/ml) cationic emulsion (IKERVIS®; Santen, Evry, France) has been shown to have prolonged pre-corneal presence and a high level of bioavailability [22–26]. The safety and efficacy profiles of ciclosporin 0.1% cationic emulsion were investigated in two randomised controlled trials; SICCANOVE (moderate-to-severe dry eye disease) and SANSIKA (severe dry eye disease), where patients showed a high level of tolerance to topical ciclosporin 0.1% and had improvements in their ocular surface inflammation [22,27–29].

The European Medicines Agency has approved ciclosporin 0.1% cationic emulsion as the first and only topical ciclosporin agent for treatment of severe OSD failing to respond to tear substitutes [22]. This has transformed the management strategies of severe and moderate-to-severe dry eye disease.

Use of ciclosporin 0.05% has been studied in patients with iatrogenic OSD secondary to chronic glaucoma medical therapy and showed improved Schirmer's test, ocular surface staining and ocular surface disease index scores [19]. However, to the best of our knowledge, there is currently no published literature around the use of ciclosporin 0.1% for treatment of OSD secondary to anti-glaucoma drops.

In this retrospective observational case series, we aim to assess the therapeutic effects of ciclosporin 0.1% in glaucoma patients with iatrogenic OSD, in whom conventional treatment has been unsuccessful.

Methods

Patients with intractable iatrogenic dry eye-related OSD secondary to anti-glaucoma drops were identified in specialist glaucoma clinics at the University Hospital of Coventry and Warwickshire (UHCW) tertiary referral centre. All patients were on long-term anti-glaucoma drops and had no improvement in their OSD despite conventional treatment measures, such as reducing anti-glaucoma drops, switching to PF formulations, the use of ocular lubricants or a course of topical steroids in addition to considering SLT,

when appropriate.

Data were collected retrospectively from electronic and paper patient records. The presence of OSD was determined based upon the subjective symptoms reported by patients and objective signs on examination. Subjective symptoms included discomfort, irritation, foreign body sensation, epiphora, subjective reduction in vision and photosensitivity. Clinical signs used were objective reduction in VA, conjunctival injection, PEEs, corneal epithelial oedema and pannus. Painless blind eyes and phthisical eyes were excluded.

All patients were referred to the specialist corneal team and started on once daily ciclosporin 0.1% eye drops in addition to their regular topical anti-glaucoma and dry eye treatments. The follow-up interval was 6–12 months. Each patient's signs and symptoms were analysed again for comparison between pre- and post-ciclosporin 0.1% treatment.

Results

Fourteen eyes of eight patients were included in this case series. Table 1 summarises the demographics of the patients. Two eyes were excluded as they were painless, blind eyes; one had a history of endophthalmitis and the other was due to advanced primary open angle glaucoma. Table 2 summaries the status of the eyes included.

All of the patients reported pain and irritation at the initial review and had corneal PEEs and conjunctival injection on examination. Figure 1 demonstrates the number of patients found to have different signs and symptoms of OSD before ciclosporin 0.1% treatment and post-ciclosporin treatment. All but one, 87.5%, of the patients reported an improvement in their OSD symptoms within 12 months of starting ciclosporin 0.1% drops, which corresponded with a clinical improvement in their ocular surface.

Table 3 provides a summary of the clinical features and outcomes for each patient pre- and post-ciclosporin 0.1% treatment. One patient (Case 5) discontinued ciclosporin 0.1% treatment due to a possible intolerance. They reported an increase in irritation on commencing treatment. However, at the follow-up clinic visit, fewer PEEs were noted with no conjunctival injection in this case. Although 6 patients (Cases 1,2,4,5,7 and 8) still had evidence of PEEs at their follow-up, this was noted to be milder than the initial visit.

Following the addition of ciclosporin 0.1%, half of all eyes achieved better VA within 12 months, with an average improvement of 0.60 to 0.20 LogMAR (Figure 2). Four eyes (28.5%) had no change in VA. Table 3 shows the clinical features, outcomes and treatment regimen before ciclosporin 0.1% initiation and during

follow-up. Three eyes (21.4%) had worse vision; 2 of these eyes were Case 5 who discontinued treatment and the other was deemed to be due to a rise in IOP and advancement of glaucoma (Case 6, left eye) as the patient showed an improvement in their signs and symptoms of OSD. The cause of the rise in IOP in this case was deemed to be due to alteration of anti-glaucoma drops rather than the addition of ciclosporin 0.1%. In all other cases, the addition of ciclosporin 0.1% did not have any adverse effects on IOP. Indeed, mean IOP was 16.6 mmHg prior to ciclosporin treatment and 15.9 mmHg post-treatment. Five patients (62.5%) continued their anti-glaucoma drops whilst on ciclosporin 0.1%. The remaining 3 patients (37.5%; Cases 2,5,7) had OSD from previous chronic use of anti-glaucoma drops and at the time ciclosporin 0.1% was started, their pressures were controlled via other means including trabeculectomy, cyclodiode, and iStent® (Glaukos, Laguna Hills, CA, USA).

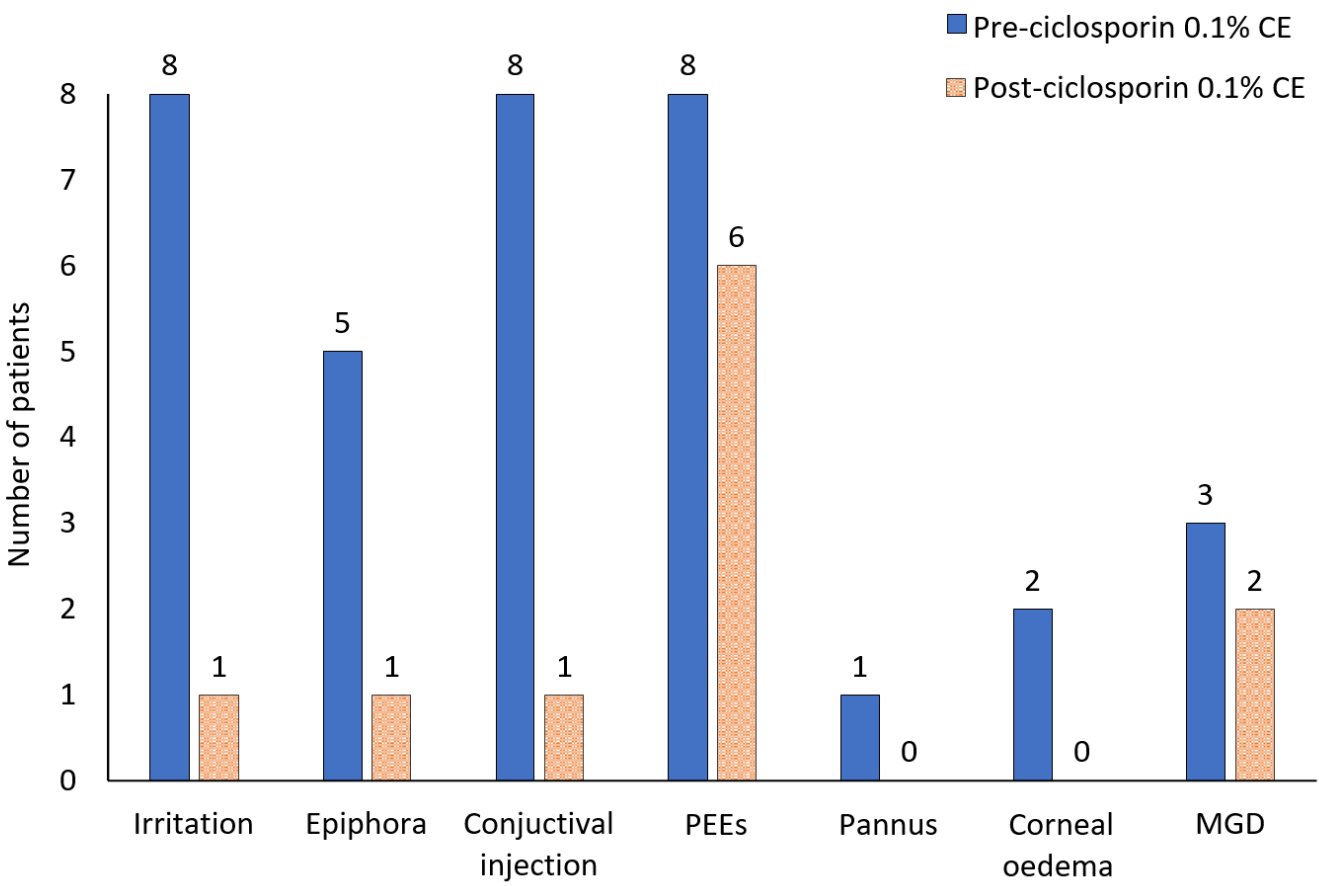

Fig 1. Clinical evaluation signs and symptoms of ocular surface disease per patient (n=8)

Abbreviations: CE, cationic emulsion; MGD, meibomian gland dysfunction; PEEs, punctate epithelial erosions.

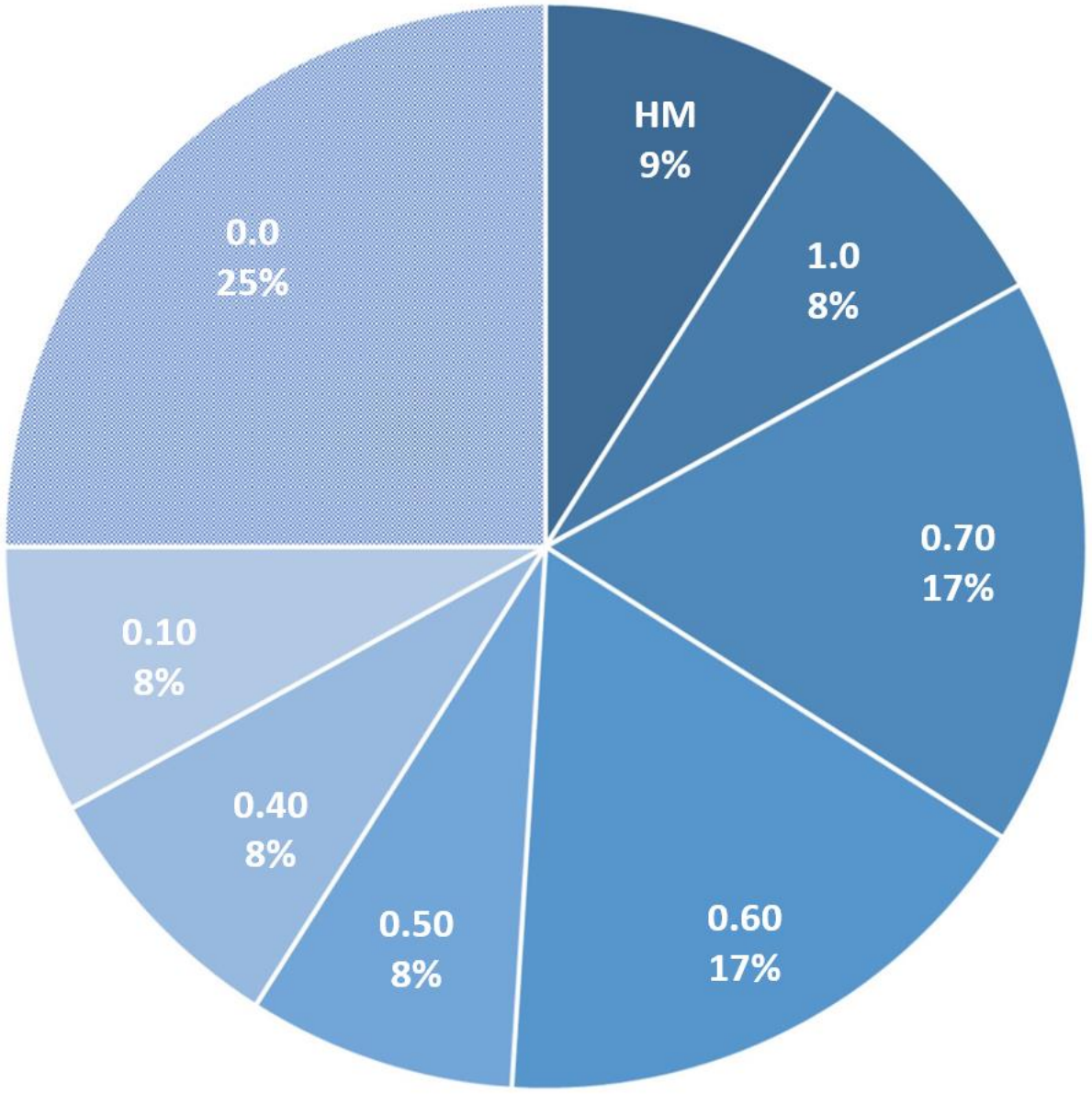

Fig 2a. Visual acuity pre-ciclosporin 0.1% eye drops (LogMAR)

Abbreviations: HM, hand movements

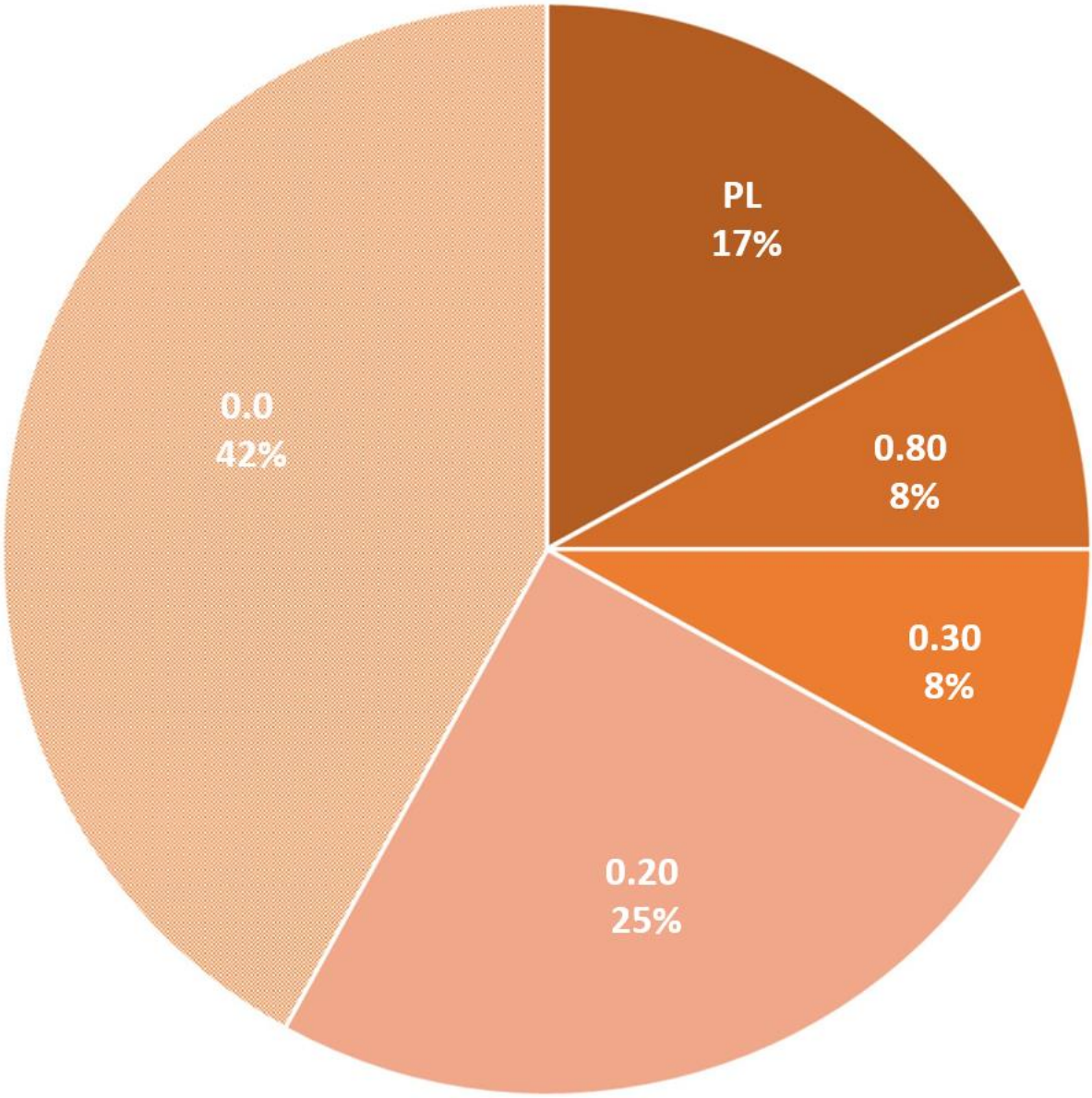

Fig 2b. Visual acuity post-ciclosporin 0.1% eye drops (LogMAR)

Abbreviations: PL, perception of light

	Patients (n = 8)
Age, years	
Mean	71
Median	72.5
Min; max	60; 80
Sex, n (%)	
Male	5 (62.5%)
Female	3 (37.5%)
Ethnicity, n (%)	
Caucasian	6 (75%)
Afro-Caribbean	0
Asian	2 (25%)

Table 1. Patient demographics

	Eyes (n = 14)
Glaucoma diagnosis, n (%)	
POAG	8 (57.1%)
NTG	2 (14.3%)
PACG	2 (14.3%)
Steroid-induced glaucoma	2 (14.3%)
Previous procedures, n	
SLT	6
Trabeculectomy	6
iStent®	2
Cyclodiode laser	2
Lens status, n (%)	
Phakic	7 (50%)
Pseudophakic	7 (50%)

Abbreviations: NTG, normal tension glaucoma; PACG, primary angle closure glaucoma; POAG, primary open angle glaucoma; SLT, selective laser trabeculoplasty.

iStent® (Glaukos, Laguna Hills, CA, USA)

Table 2. Status of eyes included

	Visual acuity (LogMAR)	**IOP (mmHg)**	**Symptoms**	**Signs**	**Initial treatment regime**	**Treatment added/altered**
Case 1						
Initial review	LE: 1.0	LE: 29	Irritation Epiphora	Severe PEEs Conjunctival injection MGD	g. Dorzolamide 2%/Timolol 0.5% PF BD g. Bimatoprost 0.01% OD	Stopped g. Bimatoprost 0.01% Started g. Latanoprost 0.005% PF OD Started g. Ciclosporin 0.1% OD Started g. Sodium hyaluronate 0.15%/ Trehalose 3% PF PRN Started g. Propylene Glycol 0.6% PRN Started g. Prednisolone Sodium Phosphate 0.5% PF 8-week course Started PO Acetazolamide 125mg QDS Started PO Doxycycline OD 100 mg 3-month course Punctal plugs inserted
Follow-up	LE: 0.20	LE: 19	Reduced irritation	Few PEEs MGD	-	Reduced PO Acetazolamide 125mg BD
Case 2						
Initial review	RE: 0.70 LE: NPL	RE: 8 LE: 30	Irritation Epiphora	PEEs MGD Conjunctival injection Pannus	g. Dexamethasone sodium phosphate 0.1% PF QDS BE g. Allogeneic serum 6 times daily BE oc. Retinol palmitate 138 µg/g/paraffin PF ON g. Sodium hyaluronate 0.2% PF 2 hourly BE	Started g. Ciclosporin 0.1% OD BE Started g. Acetylcysteine 5% PRN BE Started PO Doxycycline 100 mg 3-month course Increased g. Sodium hyaluronate 0.2% PF hourly BE
Follow-up	RE: 0.0 LE: NPL	RE: 8 LE: 30	Nil	Few PEEs	-	Stopped oc. Retinol palmitate 138 µg/g/paraffin PF ON Stopped g. Sodium hyaluronate 0.2% PF

	Visual acuity (LogMAR)	**IOP (mmHg)**	**Symptoms**	**Signs**	**Initial treatment regime**	**Treatment added/altered**
						Started g. Sodium hyaluronate 0.15%/ Trehalose 3% PF 2 hourly BE Started g. Carmellose sodium 0.5% PF PRN BE Started oc. Carbomer 0.2% PF PRN BE Reduced g. Dexamethasone sodium phosphate 0.1% PF BD BE
Case 3						
Initial review	RE: 0.70	RE: 21	Irritation	PEEs MGD Corneal epithelial oedema Conjunctival injection	PO Acetazolamide 125mg BD PO Doxycycline OD 100 mg g. Dorzolamide 2%/Timolol 0.5% PF BD g. Sodium hyaluronate 0.15%/Trehalose 3% PF 6 times daily g. Carmellose sodium 0.5% PF QDS Oc. Retinol palmitate 138 µg/g/paraffin PF ON	Stopped g. Carmellose sodium 0.5% Started g. Ciclosporin 0.1% OD Started g. Fluorometholone 0.1% BD Started g. Propylene glycol 0.6% BD
Follow-up	RE: 0.30	LE: 19	Nil	Nil	-	No changes
Case 4						
Initial review	RE: 0.50 LE: 0.10	RE: 10 LE: 17	Irritation Epiphora	PEEs Conjunctival injection	g. Levobunolol hydrochloride 0.5% BD RE g. Prednisolone sodium phosphate 0.5% PF OD RE g. Dorzolamide 2%/Timolol 0.5% PF BD LE	Started g. Ciclosporin 0.1% OD BE Started PO Doxycycline 100 mg 3-month course

	Visual acuity (LogMAR)	**IOP (mmHg)**	**Symptoms**	**Signs**	**Initial treatment regime**	**Treatment added/altered**
					g. Sodium hyaluronate 0.15%/Trehalose 3% PF QDS BE g. Carmellose sodium 0.5% PF QDS BE	
Follow-up	RE: 0.20 LE: 0.0	RE: 8 LE: 16	Nil	RE few PEEs	-	No changes
Case 5						
Initial review	RE: 0.60 LE: HM	RE: 10 LE: 20	Irritation Epiphora	PEEs Conjunctival injection	g. Carmellose sodium 1% PF 6 times daily BE	Started g. Ciclosporin 0.1% OD BE Started g. Prednisolone sodium phosphate 0.5% PF BD BE Started g. Sodium hyaluronate 0.15%/Trehalose 3% PF 2 hourly BE Started oc. Carbomer 0.2% QDS BE Punctal plugs inserted
Follow-up	RE: 0.80 LE: PL	RE: 10 LE: 12	Increased irritation	Few PEEs	-	Increased oc. Carbomer 0.2% 6 times daily BE Patient stopped all other drops
Case 6						
Initial review	RE: 0.60 LE: 0.40	RE: 14 LE: 16	Irritation Epiphora	PEEs Corneal epithelial oedema Conjunctival injection	g. Dorzolamide 2% PF BD BE g. Bimatoprost 0.01% OD BE g. Carmellose sodium 1% PF 6 times daily BE Oc. Paraffin PF ON BE PO Doxycycline OD 50 mg	Stopped g. Dorzolamide 2% PF Stopped g. Bimatoprost 0.01% Stopped g. Carmellose sodium 1% PF Started g. Latanoprost 0.005% PF OD BE Started g. Dorzolamide 2%/Timolol 0.5% PF BD BE Started g. Ciclosporin 0.1% OD BE Started g. Sodium hyaluronate 0.15%/Trehalose 3% PF 6 times a day Punctal plugs inserted
Follow-up	RE: 0.20	RE: 15 LE: 27	Nil	Nil	-	No changes

	Visual acuity (LogMAR)	**IOP (mmHg)**	**Symptoms**	**Signs**	**Initial treatment regime**	**Treatment added/altered**
	LE: PL					
Case 7						
Initial review	RE: 0.0 LE: 0.10	RE: 19 LE: 15	Irritation	PEEs Conjunctival injection	g. Sodium hyaluronate 0.15%/Trehalose 3% PF QDS BE g. Propylene glycol 0.6% BD BE PO Doxycycline OD 100 mg	Started g. Ciclosporin 0.1% OD BE
Follow-up	RE: 0.0 LE: 0.0	RE: 19 LE:15	Nil	Few PEEs	-	No changes
Case 8						
Initial review	RE: 0.0 LE: 0.0	RE: 11 LE: 12	Irritation	PEEs Conjunctival injection	g. Sodium hyaluronate 0.1%/Dexpanthenol 2% PF 6 times daily BE g. Sodium hyaluronate 0.4% PF QDS BE g. Carmellose sodium 0.5% PF PRN BE g. Travoprost 0.004%/Timolol 0.5% OD LE	Started g. Ciclosporin 0.1% OD BE Started g. Prednisolone sodium phosphate 0.5% PF BD BE Started oc. Paraffin PF ON BE
Follow-up	RE: 0.0 LE: 0.0	RE: 12 LE: 12	Nil	Few PEEs	-	No changes

Abbreviations: BD, twice daily; BE, both eyes; g., guttae; HM, hand movements; IOP, intraocular pressure; LE, left eye; MGD, meibomian gland dysfunction; NPL, no perception of light; oc., ointment; OD, once daily; ON, at night; PEEs, punctate epithelial erosions; PF, preservative free; PL, perception of light; PO, oral; PRN, as required; QDS, 4 times daily; RE, right eye; TDS, 3 times daily.

Table 3. Clinical features, outcomes and treatment regimen before ciclosporin 0.1% initiation and during follow-up

Discussion

OSD is prevalent among patients requiring long-term IOP-lowering topical therapy, particularly treatments containing BAK [5,14,15,19]. Symptoms of OSD can negatively impact a patient's quality of life, visual function and adherence to anti-glaucoma drop use [14,30]. Therapies that can successfully treat or reduce the risk of OSD in glaucoma patients are highly important for better patient outcomes.

The primary aim of this case series was to assess the therapeutic effect of ciclosporin 0.1% cationic emulsion in patients with iatrogenic OSD, secondary to long-term anti-glaucoma drops, who have failed to respond to conventional treatment. Following alteration of treatment the regimen and the addition of ciclosporin 0.1%, all patients but one reported improvement in their OSD symptoms within 12 months. On clinical examination, patients also showed less evidence of ocular surface inflammation with mean VA improving from 0.60 to 0.2 LogMAR.

One patient (Case 5) discontinued ciclosporin 0.1% treatment due to increasing symptoms of irritation. However, at the time of starting ciclosporin 0.1%, they were also initiated on prednisolone sodium phosphate 0.5% PF drops, sodium hyaluronate 0.15%/trehalose 3% PF drops and carbomer 0.2% gel. The patient stopped all treatment apart from the carbomer 0.2% gel, which was increased to 6 times a day. Therefore, it is difficult to ascertain in this situation whether there was a true intolerance to ciclosporin 0.1% or to one or more of the other treatments, or a combination of both. From the evidence available to us, we know that ciclosporin 0.1% cationic emulsion is generally well tolerated among patients with OSD [22].

Current research outlines the safety of ciclosporin 0.1% and shows no evidence that the treatment impacts IOP [27]. In our case series, the majority of patients had a stable IOP pre- and post-introduction of ciclosporin 0.1%, regardless of whether they continued concurrent use of anti-glaucoma drops or had a history of previous IOP-lowering procedures. One patient (Case 6) was started on ciclosporin 0.1% treatment for both eyes and had a unilateral spike in IOP with a decline in VA at follow-up. This was deemed to be due to alteration of anti-glaucoma drops rather than the addition of ciclosporin 0.1%. Another patient (Case 2) had elevated IOP in the left eye; a blind eye previously treated with cyclodiode before starting ciclosporin 0.1%. This eye was not excluded as the patient was reporting OSD symptoms in that eye, which improved following addition of ciclosporin 0.1% with no further rise in IOP. These findings are in keeping with other studies showing that ciclosporin 0.05% did not impact bleb function or IOP within 6 months of trabeculectomy surgery, whilst symptoms of OSD were improved [21].

Given the retrospective, observational and real-world setting of this case series, limitations were not placed upon alterations to treatment regimens that were deemed to be clinically appropriate at the initial visit. Although all patients were started on ciclosporin 0.1%, other changes were also made for all but one case (Case 7) including switching to PF formulations of IOP-lowering drops, adding/altering lubricants, starting a course of topical steroid or oral doxycycline and inserting punctal plugs. As such, we cannot infer that the majority of the patient's outcomes were solely as a result of ciclosporin 0.1% treatment, but most likely a combination of the factors. Case 7 does, however, demonstrate improved subjective and objective outcomes following addition of ciclosporin 0.1% alone. This case series therefore mimics the typical clinical use of ciclosporin 0.1% in a real-world setting. However, further study, with a larger sample size, is warranted through randomised controlled trials to investigate the sole effect of ciclosporin 0.1% on iatrogenic OSD.

In conclusion, this case series supports the suggestion that once daily ciclosporin 0.1% cationic emulsion may be considered in the treatment of iatrogenic OSD in glaucoma patients who have failed to respond to conventional treatment, particularly when there is a concern with topical steroids and a rise in IOP. To the best of our knowledge, this is the first study to examine the benefit of topical ciclosporin 0.1% cationic emulsion in glaucoma patients with OSD.

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