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Real-world experience of using ciclosporin-A 0.1% (Ikervis) in the management of ocular surface inflammatory diseases

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ABSTRACT

Purpose To report the real-world experience of using topical ciclosporin, Ikervis, in the management of ocular surface inflammatory diseases (OSIDs).

Methods This was a retrospective study of patients treated with Ikervis for OSIDs at the Queen's Medical Centre, Nottingham, between 2016 and 2019. Relevant data, including demographics, indications, clinical parameters, outcomes and adverse events, were collected and analysed for patients who had completed at least 6 months follow-up. For analytic purpose, clinical outcome was categorised as 'successful' (resolved or stable disease), 'active disease' and 'drug intolerance'.

Results 463 patients were included; mean age was 51.1±21.6 years, with a 59.0% female predominance. Mean follow-up was 14.6±9.2 months. The most common diagnosis was dry eye disease (DED; 322, 69.5%), followed by allergic eye disease (AED; 53, 11.4%) and ocular mucous membrane pemphigoid/Steven-Johnson syndrome (OMMP/SJS; 38, 8.2%). Successful treatment was achieved in 343 (74.1%) patients, with 44 (9.5%) requiring additional treatment and 76 (16.4%) reporting drug intolerance. The efficacy of Ikervis was highest in DED (264, 82.0%), followed by OMMP/SJS (25, 65.8%) and post-keratoplasty (7, 50.0%; p<0.001). Logistic regression analysis demonstrated age <70 years (p=0.007), AED (p=0.002) and OMMP/SJS (p=0.001) as significant predictive factors for Ikervis intolerance. AED and post-keratoplasty were 8.16 times (95% CI, 2.78 to 23.99) and 13.98 times (95% CI, 4.22 to 46.28), respectively, more likely to require additional treatment compared with DED.

Conclusions Ikervis is a useful steroid-sparing topical treatment for managing OSIDs in the real-world setting. Preparations with improved tolerability are needed to benefit a larger number of patients.

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INTRODUCTION

Dry eye disease (DED) is the most common disease affecting the ocular surface (OS) in the young and old, increasing with age, with a female preponderance.[1 2] There are various reports on the incidence and prevalence of DED, which is estimated to affect 15%–33% of individuals aged over 65 years but younger individuals are increasingly being affected.[2–4] DED is traditionally classified as aqueous deficient DED (resulting from affection of the lacrimal gland) or evaporative DED (primarily due to meibomian gland dysfunction), though increasingly a considerable overlap between the two is being recognised.[5] Many factors operate in the aetiology and pathophysiology of DED of which inflammation was first recognised as an important and consistent component in the report published following a Delphi approach to treatment recommendations in 2006[6] and substantiated in subsequent reports.[7 8]

Steroids have been the mainstay in the management of most inflammatory conditions, including DED, allergic eye disease (AED), chemical eye injury, ocular mucous membrane pemphigoid (OMMP), Steven-Johnson syndrome (SJS) and many others.[9] However, over the last two decades, non-glucocorticoid immune-modulators, especially ciclosporin A (CsA), have gained prominence as steroid-sparing topical therapy for DED.[10 11] Oil-based CsA preparations were in vogue (Optimmune 0.2%, licenced for dogs) and used off-label in humans since the 1980s. Restasis (0.05% CsA, Allergan, California, USA) was approved and licenced by the Food and Drug Administration (FDA), USA, for treatment of DED in 2002.[12] However the drug was not available in Canada and Europe including the UK, and the market authorisation application to the European Medicines Agency (EMA) was withdrawn by Allergan in 2018.[13] In 2015 Ikervis, a CsA eye-drop preparation (1 mg/mL or 0.1%) was approved by the EMA for the treatment of severe DED in adults and by the National Institute for Health and Care Excellence, UK, for the treatment of severe keratitis of DED not responding to treatment with tear substitutes.[14 15] In 2018, the same preparation of CsA as in Ikervis (recommended once daily for DED) was marketed with a different packaging, under the name of Verkazia (recommended four times a day) after being approved by EMA for treatment of severe vernal keratoconjunctivitis (VKC).[16]

As the only licenced steroid-sparing anti-inflammatory agent available for direct treatment at the OS, the incentive and clinical pressure to use it for other inflammatory conditions was considerable, and as often happens in clinical practice, off-label use of Ikervis became an option in a variety of clinical scenarios where previous oil-based preparations of CsA were used with some or significant benefit.[17 18] We report our real-world experience with licenced and off-label use of Ikervis in the management of chronic non-infective OS inflammatory diseases (OSIDs).

MATERIALS AND METHODS

A list of patients who received a prescription of Ikervis (topical CsA 0.1%) from April 2016 to October 2019 was obtained from the hospital pharmacy database. All the charts were retrospectively analysed and patients who had a follow-up of more than 6 months were included in the study. An Excel spreadsheet was created to standardise the data collection, which included the demographic profile, diagnosis, clinical parameters, dose and duration of Ikervis treatment and clinical outcome. Diagnosis was based on clinical examination, characteristic findings and biopsy (where applicable). Patients were categorised into DED, AED including VKC and atopic keratoconjunctivitis (AKC), OMMP, SJS and post-keratoplasty cases. Diagnoses other than these were categorised as 'others'. These patients included non-specific chronic conjunctivitis, limbal stem cell deficiency, neurotrophic keratopathy, inflammatory keratitis like superior limbic keratitis, inflamed pterygium or pseudopterygium, peripheral ulcerative keratitis and scleritis/episcleritis. Clinical parameters noted included best corrected visual acuity at baseline and final follow-up visit or at the time of discontinuing Ikervis, whichever was sooner, intraocular pressure, conjunctival findings, corneal findings, dry eye parameters like tear-film breakup time and Schirmer's test II values were recorded. A note was made when patients presented with burning sensation or ocular discomfort affecting compliance. When Ikervis was discontinued by the treating physician within a duration of 6 months, owing to the side effects or patient intolerance, patients were not excluded but were categorised under the intolerant group when evaluating the clinical outcome.

Clinical outcome was defined based on clinical parameters on follow-up as: (1) resolved: when the signs and symptoms subsided completely for at least 1 month with no requirement of further Ikervis treatment; (2) stable: when the disease did not resolve nor worsened with ongoing Ikervis and the OS (defined as the conjunctiva, cornea and lacrimal apparatus) was free from visibly detectable inflammation and/or graft rejection (in post-keratoplasty cases); (3) active: flare up of condition or active inflammation requiring additional treatment such as topical steroids and (4) intolerant: when patient on Ikervis experienced burning sensation and discomfort necessitating discontinuation of the drug. The treatment was considered a 'success' if outcome 1 (resolved) or outcome 2 (stabilised) were achieved.

Statistical analysis

Statistical analysis was performed using SPSS Statistics V.26 (IBM SPSS Statistics for Windows). Comparison between groups was conducted using Pearson's χ^2 or Fisher's Exact test where appropriate for categorical variables, and unpaired t-test or Mann-Whiney U test for continuous variables. Normality of data distribution was assumed if the skewness and kurtosis z-values were between −1.96 and +1.96 and the Shapiro-Wilk test p value was >0.05. All continuous data were presented as mean±SD. Multivariable logistic regression analysis was conducted to determine: (1) the likelihood of patients experiencing intolerable side effects of Ikervis; and (2) the likelihood of patients requiring additional treatment, particularly topical steroids, while on Ikervis. For analysis, the diagnosis was categorised into five groups, namely (1) DED, (2) AED, which included VKC and AKC, (3) OMMP/SJS, (4) post-keratoplasty and (5) others.

P value of ≤0.05 was considered statistically significant. When multiple subgroups were analysed, crude Bonferroni-type adjustment was used to keep the overall false positive rate or alpha level at 0.05 (eg, if comparison of 5 subgroups was performed, the adjusted p value of ≤0.01 (based on 0.05/5) was considered significant).

Table 1 Summary of the characteristics of patients treated with topical ciclosporin (Ikervis) in Nottingham, UK

	Total n=463
Parameters	**n (%)**
Age, years	
0–18	34 (7.3)
>18 to 30	44 (9.5)
>31 to 50	98 (21.2)
>51 to 70	152 (32.8)
>70	135 (29.2)
Gender	
Female	273 (59.0)
Male	190 (41.0)
Diagnosis	
Dry eye diseases	322 (69.5)
AED	53 (11.4)
OMMP	28 (6.0)
Post-corneal graft	14 (3.0)
SJS	10 (2.2)
Others*	36 (7.8)
CDVA, logMAR	
Baseline	0.24±0.45
Final	0.23±0.47
Clinical outcome†	
Resolved	119 (25.7)
Stable	224 (48.4)
Active	44 (9.5)
Intolerant to Ikervis	76 (16.4)
Treatment frequency	
Once a day	286 (61.8)
Twice a day	173 (37.4)
>Twice a day	4 (0.9)
Follow-up duration, months	14.6±9.2

*Included cases of inflammatory keratitis (n=9), non-specific chronic conjunctivitis (n=7), scleritis/episcleritis (n=4), limbal stem cell deficiency (n=3), neurotrophic keratopathy (n=2), pseudopterygium (n=2), peripheral ulcerative keratitis (n=2), superior limbic keratoconjunctivitis (n=2), uveitis (n=2), epithelial ingrowth (n=1), conjunctival granuloma (n=1) and giant papillary conjunctivitis (n=1).
†Clinical outcome is defined as: (1) resolved: resolution of disease without further need of Ikervis; (2) stable: stable disease with ongoing Ikervis; (3) active: active disease requiring additional treatment such as topical steroids and (4) intolerant: Ikervis discontinued due to intolerable side effects.
AED, allergic eye disease (which included vernal keratoconjunctivitis and atopic keratoconjunctivitis; CDVA, corrected distance visual acuity; OMMP, ocular mucous membrane pemphigoid; SJS, Steven-Johnson syndrome.

RESULTS

A total of 463 patients were included in this study; the mean age was 51.1±21.6 years, with a 59.0% (n=273) female predominance. The mean follow-up duration was 14.6±9.2 months. The most common diagnosis was DED (322, 69.5%), followed by AED (53, 11.4%) and OMMP/SJS (38, 8.2%; table 1). Of all patients, 343 (74.1%) patients were successfully treated with Ikervis. Forty-four (9.5%) required additional treatment such as topical steroids and 76 (16.4%) discontinued due to intolerance to Ikervis. The majority of patients received once a day (286, 61.8%) Ikervis treatment, followed by twice a day (173, 37.4%) and more than twice a day (4, 0.9%). Summary and details of

Table 2 Summary of clinical outcome of all patients who received Ikervis and the dosing frequency used, categorised into five indications (total n=463 patients)

	DED	AED	OMMP/SJS	Post-graft	Others	
	Total n=322	Total n=53	Total n=38	Total n=14	Total n=36	
	n (%)	n (%)	n (%)	n (%)	n (%)	P value*
Outcome						
Resolved	98 (30.4)	6 (11.3)	1 (2.6)	1 (7.1)	13 (36.1)	<0.001
Stable	166 (51.6)	14 (26.4)	24 (63.2)	6 (42.9)	14 (38.9)	<0.001
Active	21 (6.5)	11 (20.8)	2 (5.3)	7 (50.0)	3 (8.3)	<0.001
Intolerant	37 (11.5)	22 (41.5)	11 (28.9)	0 (0.0)	6 (16.7)	<0.001
Ikervis frequency						0.007†
Once a day	212 (65.8)	28 (52.8)	21 (55.3)	3 (21.4)	22 (61.1)	
Twice a day	110 (34.2)	23 (43.4)	17 (44.7)	9 (64.3)	13 (36.1)	
>Twice a day	0	1 (1.9)	0	2 (1.43)	1 (2.8)	
Treatment duration, months‡	12.1±6.4	18.7±8.1	10	24	11.5±10.4	0.08

*Comparison was made among the five indications for each clinical outcome.
†χ^2 test was performed to compare the difference among the five indications between group 1 (once a day group) and group 2 (twice a day and >twice a day groups).
‡Treatment duration, presented in mean±SD, refers to the duration of Ikervis used to achieve resolution of the disease. ANOVA test was performed to examine the difference among DED, AED and others groups.
AED, allergic eye disease (which included vernal and atopic keratoconjunctivitis; DED, dry eye disease; OMMP, ocular mucous membrane pemphigoid; SJS, Steven-Johnson syndrome.

dosing according to the different groups are provided in tables 1 and 2.

There was a significant difference in the clinical outcome, tolerability and dosing frequency of Ikervis among the five groups of indications (table 2). The efficacy of Ikervis (including both 'resolved' and 'stable' group) was shown to be highest in patients with DED (264, 82.0%), followed by OMMP/SJS (25, 65.8%), post-keratoplasty (7, 50.0%) and AED (20, 37.7%; p<0.001). Intolerable side effects of Ikervis were most commonly experienced in patients with AED (22, 41.5%), followed by OMMP/SJS (11, 28.9%) and DED (37, 11.5%; p<0.001). When the group of patients who did not tolerate Ikervis was excluded from the analysis, Ikervis was shown to achieve successful control in 264 (92.6%) cases of DED, 25 (92.6%) cases of OMMP/SJS and 20 (64.5%) cases of AED, though 7 (50%) cases of the post-keratoplasty patients required additional treatment such as topical steroids (table 3).

Logistic regression analysis demonstrated that patients who were more than 70 years old were significantly less likely to experience intolerable side effects of Ikervis as compared with other age groups (table 4). When compared with DED, patients with AED and OMMP/SJS were 3.81 times (95% CI, 1.79 to 8.11) and 3.81 times (95% CI, 1.65 to 8.82) more likely to experience intolerable side effects of Ikervis, respectively. Ikervis treatment frequency did not show any significant influence on the drug tolerability (p=0.79).

After excluding 76 patients who experienced intolerable side effects of Ikervis, a total of 387 patients were included in the analysis of the clinical outcome. When compared with DED, logistic regression analysis showed that AED and post-keratoplasty patients were 9.18 times (95% CI, 3.01 to 27.94) and 9.59 times (95% CI, 2.66 to 34.57), respectively, more likely to require additional treatment such as topical steroids (table 5). Patients who received twice a day Ikervis treatment were more likely to require additional treatment than those who received once a day Ikervis treatment (p=0.04).

DISCUSSION

'Dry eyes' is both a symptom and a diagnosis. A symptom, reflecting the subjective sensation experienced by the patient and a diagnosis by virtue of the label assigned to the condition based on clinical signs, such as narrow tear meniscus, rapid tear film break-up time and punctate OS erosions; with or without the support of tests ranging from the Schirmer's test to in vivo confocal microscopy of the corneal epithelium and impression cytology of the OS.[19–21] The nomenclature is varied with 'DED' being the most popular but terms such as keratoconjunctivitis sicca, xerosis ophthalmia and others are also used with the same connotation. Arguably DED is not one condition but a common downstream manifestation of a host of local or systemic diagnoses. In addition, disruption of the homeostasis of the OS induced by ocular surgery could also trigger or exacerbate the manifestation of DED, leading to potentially sight-threatening complications.[22–24] DED related to laser refractive surgery, connective tissue diseases, menopause, graft versus host

Table 3 Summary of clinical outcome of all patients who received and tolerated Ikervis treatment, categorised into five indications (total n=387 patients)

Clinical outcome	DED Total n=285; n (%)	AED Total n=31; n (%)	OMMP/SJS Total n=27; n (%)	Post-graft Total n=14; n (%)	Others Total n=30; n (%)	P value*
Resolved/stable	264 (92.6)	20 (64.5)	25 (92.6)	7 (50.0)	27 (90.0)	<0.001
Active	21 (7.4)	11 (35.5)	2 (7.4)	7 (50.0)	3 (10.0)	

*Comparison was made among the five indications.
AED, allergic eye disease (which included vernal keratoconjunctivitis and atopic keratoconjunctivitis; DED, dry eye disease; OMMP, ocular mucous membrane pemphigoid; SJS, Steven-Johnson syndrome.

Table 4 Logistic regression analysis for predicting the likelihood of patients experiencing intolerable side effect of topical ciclosporin/Ikervis (total n=463 patients)

Parameters	OR (95% CI)	P value
Age, years		0.006
0–18	3.57 (1.03 to 12.43)	0.045
>18 to 30	7.50 (2.52 to 22.31)	<0.001
>31 to 50	3.30 (1.23 to 8.87)	0.018
>51 to 70	4.12 (1.69 to 10.04)	0.002
>70	Reference	–
Gender		
Female	0.99 (0.57 to 1.71)	0.97
Male	Reference	–
Indications		0.001
Dry eye disease	Reference	–
AED	3.81 (1.79 to 8.11)	0.001
OMMP/SJS	3.81 (1.65 to 8.82)	0.002
Post-keratoplasty*	–	–
Others	1.34 (0.51 to 3.50)	0.55
Treatment frequency		
Once a day	Reference	–
Twice a day	1.08 (0.63 to 1.85)	0.79
>Twice a day*	–	–

*No patient experienced intolerable side effect in this group and therefore analysis was not possible.
AED, allergic eye disease (which included vernal keratoconjunctivitis and atopic keratoconjunctivitis; OMMP, ocular mucous membrane pemphigoid; SJS, Steven-Johnson syndrome.

Table 5 Logistic regression analysis for predicting the likelihood of patients requiring additional topical steroids while being treated with topical ciclosporin/Ikervis (total n=387 patients). Patients who were intolerant to the Ikervis were excluded from this analysis

Parameters	OR (95% CI)	P value
Age, years		0.04
0–18	0.62 (0.12 to 3.19)	0.56
>18 to 30	3.02 (0.86 to 10.61)	0.09
>31 to 50	0.44 (0.13 to 1.55)	0.2
>51 to 70	1.59 (0.64 to 3.94)	0.32
>70	Reference	–
Gender		
Female	0.78 (0.37 to 1.65)	0.52
Male	Reference	–
Indications		<0.001
Dry eye disease	Reference	–
AED	9.18 (3.01 to 27.94)	<0.001
OMMP/SJS	0.90 (0.19 to 4.18)	0.89
Post-keratoplasty	9.59 (2.66 to 34.57)	0.001
Others	1.27 (0.34 to 4.78)	0.72
Treatment frequency		0.016
Once a day	Reference	–
Twice a day	2.86 (1.39 to 5.90)	0.04
>Twice a day	3.19 (0.29 to 35.25)	0.34

AED, allergic eye disease (which included vernal keratoconjunctivitis and atopic keratoconjunctivitis; OMMP, ocular mucous membrane pemphigoid; SJS, Steven-Johnson syndrome.

disease, cicatrising conjunctivitis or old age may have similar characteristic symptoms and signs but are clearly not the same disease entity. The term 'dysfunctional tear syndrome' though less popular, is more apt.[6]

The first global attempt at a unified definition of DED was made in 1995 by the National Eye Institute/Industry working group on Clinical Trials in Dry Eye.[25] This definition did not include the term 'inflammation'. In the years that followed evidence appeared in the literature to demonstrate the key role played by inflammation in DED and it became recognised as an inflammatory disorder,[10 11] which was reflected in the publication by Behrens *et al*,[6] in the international consensus definition of DED. The word 'inflammation' was incorporated in the definition of DED, proposed and published by the Dry Eye Workshops I and II.[5 7] The latter added 'neurosensory abnormalities' to the definition to emphasise the role played by damage to OS innervation, including nerve inflammation, in DED.[5]

Anti-inflammatory agents were added to the variety of medications used to treat DED. Steroids were the obvious choice but with known complications associated with their long-term use. CsA 0.2%, under the name of 'optimmune', has been used by veterinary colleagues to treat DED in dogs since the early 1990s.[26–28] CsA in varying concentrations, notably Restasis, and more recently Cequa (CsA 0.09%, Sun Pharma, Cranbury, NJ, USA), in 2018, has also been used to treat a variety of OS inflammatory diseases including DED.[12 14]

CsA is a lipophilic cyclic polypeptide derived from the fungus, Hypocladium inflatum gams. Its major immunomodulatory activity relates to its effect on calcineurin. Calcineurin, a cytosolic protein, is a serine/threonine phosphatase enzyme, the activity of which is regulated by calcium/calcium-binding messenger protein (calmodulin) and is important in the activation of T lymphocytes. Calcineurin, in a calcium dependent manner, dephosphorylates nuclear factor(s) of activated T cells (NFAT proteins) allowing them to translocate to the nucleus where they activate gene expression of cytokines. CsA binds to ubiquitous cytosolic proteins called cyclophilins. Cyclophilin–CsA complex binds to calcineurin and inhibits calcineurin-mediated dephosphorylation thus blocking the nuclear translocation of NFAT protein, thus preventing gene expression and transcription of several cytokines, in particular interleukin-2, involved in differentiation and survival of T helper cells.[29 30]

Ikervis is a 0.1% (1 mg/mL), sterile, unpreserved, oil-in-water emulsion of CsA. The eye drops also contains the cationic agent, cetalkonium chloride (CKC), which increases the resident time of the drops on the OS. Its anti-inflammatory effect covers the OS and the lacrimal gland. The same preparation, in a different presentation format and licensed for use in children (above 4 years) at a frequency of four times a day to treat VKC, is called Verkazia.[16] When we started our patients with Ikervis, Verkazia was not in the market. We did however treat our patients with VKC with Ikervis at a frequency of 2–4 times a day and noticed good efficacy but unfortunately comparatively poor tolerability. Our results are consistent with the VEKTIS (VErnal KeratoconjunctiviTIs Study) study that analysed the efficacy of topical CsA 0.1% in severe VKC. The authors reported successful use of high dose CsA (four times a day) in controlling acute symptoms of VKC thereby reducing the need of rescue drugs in nearly one-third of each high-dose and low-dose group.[31] However, it is to be noted that the VEKTIS Study analysed only paediatric patients with severe VKC. In the current study, we have analysed patients with VKC or AED in all age groups.

Twice as many patients with AED had resolved or were stable compared with those that needed additional treatment.

Unfortunately, the number that were intolerant were as many as those who benefitted. If the tolerance of the medication could be improved, the data suggest that many more patients of AED would benefit. It is not clear why patients in the older age group tolerated the drug better than those in the younger age group. It could well be due to the difference in pain threshold of these two populations of individuals or sensitivity to excipients including CKC. A future longitudinal study will address these effects. AED patients also had a greater frequency of instillation compared with the DED group but so did the OMMP/SJS and 'others' groups where tolerability was better. Technically speaking, the use of Ikervis for treatment of VKC, through the course of this study, would be off-label. DED was the only licensed indication and also the one that showed the best outcome in that 82% of patients had resolved or were stable and maintained on the medication. This group also had the best tolerance, with only 11.5% having to withdraw treatment due to intolerance. Our study demonstrated comparable results in DED patients as the SANSIKA Study in which 29.2% patients reported pain on instillation with 12.3% having moderate to severe pain.[32] Since the use of CsA 0.1% in DED is established, we used DED as a comparator for the other conditions treated.

Other main OS inflammatory conditions where Ikervis was used off-label, were OMMP, SJS and 'others'. As illustrated in table 3, if patients who did not tolerate the drug (hence efficacy could not be determined) are excluded; more patients benefitted relative to those who did not. Overall, it was encouraging to see that the majority of patients in these groups benefitted on treatment with Ikervis, making it a viable steroid-sparing option for controlling inflammation manifest at the OS, negating the long-term risks of steroid induced secondary rise in intraocular pressure and cataract.[33] Use of topical ciclosporin in high risk grafts to prevent graft rejection has been described. In 2004, the Cornea Society Survey revealed that 48% clinicians used topical CsA in high risk keratoplasties.[34] The evidence of the benefits of topical CsA has been inconsistent.[35] Although a few studies have described improvements in rejection-free rates and graft survival,[36–38] majority of the studies have not been able to demonstrate any benefit of the use of topical CsA.[39–41] Theoretically, Ikervis could be a potentially useful alternative in corneal transplant patients who were 'steroid responders'. Unfortunately, this was not borne out in this study as the efficacy in managing or controlling rejection was not significant, with half the patients requiring additional steroid medication. However, the number of patients was too small for a meaningful conclusion to be drawn and a further study of this group of patients with Ikervis is warranted to determine appropriate frequency and duration of instillation, and efficacy. Use of topical CsA has been shown to be of benefit in OMMP/SJS cases.[42 43] Our study showed that patients with OMMP/SJS were almost as likely to require additional topical steroids as DED patients and were more intolerant to Ikervis. Stable OS was achieved in 63.2% cases, however the sample size was small and larger studies are required to establish the efficacy and tolerance of Ikervis in these patients.

Based on this study of our real-world experience, we would recommend that all non-infective chronic OS inflammatory diseases be treated with a short course of preservative free topical steroid medication and then switch to CsA drops when a response is induced. Those that develop a relapse would require additional medication with or without the continuation of CsA. This approach will also identify initial steroid non-responders where CsA alone is unlikely to help and where systemic immunosuppressive agents may be required to induce a remission. In this study, overall 74% of patients benefitted and 16% showed intolerance across all groups. Improving tolerance of future preparations of CsA could improve the overall efficacy.

The natural course of the chronic conditions included in this study is characterised by relapses and remissions. When an acute episode was treated and resolved sufficient to discharge the patient it was taken as the end point. Hence the term 'resolved' is used as defined in the Methods section and does not equate to a cure. The large number of patients, the long mean follow-up duration, the real-world experience and the identification of the outcomes to be expected in different groups of inflammatory conditions are important strengths of the study. However, there are some limitations. As this was a retrospective study, it was difficult to capture quantitatively the data for all 463 patients. The lack of definitive quantitative data related to all the parameters of DED and inflammation is a limitation. The inherent limitations of a retrospective study, related to use of other topical and particularly systemic medications also apply to this study though we have analysed and presented concomitant use of steroid drops. In modern day clinical practice, cost is an important issue and cost benefit analysis is increasingly being taken into consideration for approval of drugs funded by the public purse. Such an analysis for Ikervis was beyond the scope of this study.

As the incidence and prevalence of DED affecting younger and older patients is ever increasing, the quest for alternative treatments continues. New studies on immunomodulation of OS inflammation place emphasis on novel drug delivery or mechanisms targeting T-cells. Cequa (CsA 0.09%) is a nanomicellar ciclosporin formulation that enables improved drug penetration achieving drug concentrations in conjunctival and corneal cells, however, symptoms of stinging and pain continue to be reported in 22%.[44] OTX-CSI is a long-acting, preservative-free ciclosporin intracanalicular hydrogel insert designed to deliver ciclosporin up to 12 weeks while also occluding the lower punctum is currently being evaluated in a Phase I/II safety and tolerability study. Lifitegrast, an integrin antagonist that blocks the interaction of lymphocyte function-associated antigen-1 (LFA-1) / intercellular adhesion molecule-1 (ICAM-1)inhibiting T-cell activation and release of pro-inflammatory cytokines, is FDA approved as 5% ophthalmic solution (Xiidra) for use in DED. While this shows some promise, it currently does not have global marketing authorisation.[45]

The immune system is fundamental to the survival of the host against environmental onslaughts from a multitude of agents both innate and living. It has evolved and adapted through evolution into a very complex system that can deal with current and potential future antigens. The approaches adopted above by targeting a single molecule are probably inadequate. The plethora of molecules, the interlinked pathways, the redundancy and ability to constantly adapt imply that no single molecule in the immune system is indispensable. Targeting a single specific key molecule may contain an immune response (inflammation) for a varying period of time but unlikely to make a permanent impact. Perhaps this is why the results of studies are so variable, often conflicting, with some patients responding, some responding for some time and others not at all.

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Patient consent for publication Not required.

Ethics approval The study was approved as a healthcare improvement audit by the Clinical Audit and Effectiveness Department of the Nottingham University Hospitals National Health Service (NHS) Trust, Nottingham, UK (Project number: 19-443C).

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