

Steroid-sparing effect of ciclosporin A 1 mg/mL: 5-year case series of 107 children and young people with vernal keratoconjunctivitis

Annegret Hella Dahlmann-Noor ,^{1,2} Clare Roberts,² Kirithika Muthusamy,² Virginia Calder,³ Melanie Hingorani²

To cite: Dahlmann-Noor AH, Roberts C, Muthusamy K, *et al*. Steroid-sparing effect of ciclosporin A 1 mg/mL: 5-year case series of 107 children and young people with vernal keratoconjunctivitis. *BMJ Open Ophthalmology* 2022;**7**:e001040. doi:10.1136/bmjophth-2022-001040

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjophth-2022-001040>).

Received 12 April 2022
Accepted 14 September 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹NIHR Moorfields Biomedical Research Centre, London, UK

²Children's Service, Moorfields Eye Hospital NHS Foundation Trust, London, UK

³UCL Institute of Ophthalmology, London, UK

Correspondence to

Dr Annegret Hella Dahlmann-Noor; annegret.dahlmann-noor@nhs.net

ABSTRACT

Background/aims To explore the steroid-sparing and other therapeutic effects of ciclosporin A (CsA) 1 mg/mL in the management of vernal keratoconjunctivitis (VKC).

Methods Open retrospective single-group interventional consecutive cohort study (case series) of 107 children and young people (CYP) age 4.4–18 years with severe and/or recurrent VKC who were prescribed CsA 1 mg/mL between November 2015 and May 2021 at one institution. Review of electronic patient records, noting clinical indication for prescribing CsA 1 mg/mL, dosage prescribed at initiation and follow-up, impact on steroid usage before and after commencing CsA as well as adverse events and indications for discontinuation of treatment.

Results The median number of inflammatory episodes requiring treatment with topical corticosteroids fell from 3 (IQR 2–4) during the 12 months prior to CsA 1 mg/mL to 1 (IQR 0–3) during the 12 months after, excluding steroid prescriptions with the first CsA 1 mg/mL prescription (Wilcoxon signed ranks test, two tailed, $p < 0.01$). In the 12-month period following initiation of CsA 1 mg/mL with concomitant prescription of topical corticosteroids ($n = 82$), daily dosage of steroids was reduced in 79 (96.3%) and discontinued in 67 (81.7%). The median number of hospital clinic visits fell from 4 (IQR 3–5) to 3 (IQR 2–5) (Wilcoxon $p < 0.01$). Adverse events leading to discontinuation of CsA 1 mg/mL within 12 months of starting included stinging (instillation site pain) (6/107, 5.6%) and skinrash (1/107, 0.9%).

Conclusion Commercial preparations of CsA 1 mg/mL, licensed for severe VKC in CYP, significantly reduce the need for concomitant topical corticosteroids and hospital clinic visits. Adverse events which may lead to discontinuation are stinging and skin rash.

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a severe allergic hypersensitivity disorder of the ocular surface which predominantly affects children and young people (CYP) and has potential sight-threatening corneal complications.¹ Frequent and long-term use of topical corticosteroids (tCS) to control vernal inflammation

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Randomised controlled trials have demonstrated efficacy and safety of topical ciclosporin A monotherapy in the management of vernal keratoconjunctivitis (VKC), but its role in real-life management algorithms, where topical corticosteroids are often prescribed concomitantly, has not been explored.

WHAT THIS STUDY ADDS

⇒ Topical ciclosporin A reduces the need for hospital visits and concomitant topical corticosteroids to induce and maintain control of ocular surface inflammation in VKC. Adverse events that can lead to discontinuation include stinging and skin rash.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Following initiation of topical ciclosporin A by a hospital eye care professional, general practitioners can provide maintenance prescriptions. Families may titrate daily dosage against severity of symptoms, which frequently show seasonal variation. Hospital and general practitioners and families working together can improve the quality of life of young people with VKC and their families, reducing the burden of the condition, the frequency of hospital visits and the risk of adverse events related to topical corticosteroids.

can lead to cataract and secondary glaucoma due to steroid-induced raised intraocular pressure (IOP).² In November 2015, a commercial preparation of topical ciclosporin A (CsA) 1 mg/mL (Ikervis, Santen) licensed for twice daily application for severe keratitis in adults with dry eye disease, was included in our institution's formulary, and we began to use it off-label in CYP with VKC. In September 2018,^{3 4} a licensed paediatric product of the same formulation of CsA 1 mg/mL was introduced (Verkazia, Santen) for four times daily application in severe VKC.^{3 4} Hospital specialist-initiated prescription of the licensed medication could now be continued

by the family practitioner. Both the steroid-sparing effect of CsA and the initiation of community prescribing could potentially have a profound effect on the management of VKC in CYP.

A constraint of the pivotal randomised controlled trial was that concomitant prescription of tCS was not permitted, as the trial aimed to assess efficacy of CsA 1 mg/mL monotherapy.^{3 4} tCS usage was allowed as rescue medication only.^{3 4} However, as CsA typically takes 2–4 weeks to develop full efficacy, clinicians in practice frequently prescribe a short concomitant course of tCS to achieve rapid control of acute signs and symptoms.⁵ The lack of real-world data on the steroid-sparing effect of CsA 1 mg/mL are highlighted by recent systematic reviews and meta-analyses of the management of allergic eye disease.^{6 7}

Drawing on our experience with CsA 1 mg/mL in the treatment of VKC in CYP since 2015 (in the following referred to as CsA), we carried out a review of patient records to identify the real-world effects on concomitant use of tCS, the need for hospital clinic visits, and circumstances leading to discontinuation of treatment, including adverse events.

MATERIALS AND METHODS

The present work is an open retrospective single-group interventional consecutive cohort study/case series, carried out at a single institution in London, UK, which offers secondary and tertiary care for CYP with VKC.

On 29 May 2021, we carried out a search of electronic medical records and pharmacy prescriptions of patients aged 18 years or younger at our facility, using the terms ‘ciclosporin/e’, ‘ciclosporin/e’, ‘Ikervis’ and ‘Verkazia’. In order to identify cases of VKC, we used the following clinical case definition^{1 8 9}: ocular surface inflammation with tarsal papillary hypertrophy, limbal inflammation with Horner Trantas dots, corneal punctate epitheliopathy/macroerosion/plaque/shield ulcer, symptom of eye itching (pruritus), and absence of atopic dermatitis and significant meibomian gland disease. We excluded those CYP who received CsA for atopic keratoconjunctivitis (atopic dermatitis and/or significant meibomian gland disease with allergic ocular surface inflammation including signs and symptoms as listed for VKC),^{1 8} and those with blepharokeratoconjunctivitis (ocular surface inflammation with signs of meibomian gland dysfunction and inflammation such as inspissation (bulging) of MG orifices, chalazia, lid margin inflammation/telangiectasia/thickening/distortion/keratinisation, lash collarettes/crusting, conjunctival phlycten, tarsal/lower fornix follicular inflammation and absence of eye itching, tarsal papillary hypertrophy and atopic dermatitis)¹⁰ or other types of ocular surface inflammation. In order to minimise selection bias, we included all consecutive cases which met the above criteria. The number of cases treated during the observation period determined the sample size. We included in our dataset CYP who started using CsA 1 mg/mL between November 2015

and May 2021, and then used it continuously or intermittently. Between 2015 and September 2018, we used Ikervis off-label and, from September 2018, Verkazia. We included follow-up information collected until the end of October 2021. Until 2020, our institution operated a hybrid medical record system, the electronic system being used to generate reports for family doctors and parents/carers, while some details of clinical assessments tended to be recorded in handwritten paper-based notes. For this study, we only reviewed the electronic records, as important information such as clinically significant rises in IOP would be transferred onto the electronic record.

We extracted relevant data onto a predesigned Microsoft (Redmond, USA) Office Excel spreadsheet. The main outcome measures are the number of prescriptions for tCS and hospital clinic visits over 12 months before and after start of CsA and the occurrence of adverse effects leading to discontinuation of treatment. We recorded demographic and clinical data: age at start of treatment, gender, indication, calendar year and dosage at start of treatment, minimum and maximum prescribed daily dosage during first and every subsequent year of treatment, date of discontinuation of CsA, reason for discontinuation, doctor or family discontinuing CsA, restarting of CsA and reason to restart. The unit of analysis was the child. Over time, all cases were bilateral, though sometimes inflammation and treatment dosage were asymmetrical. Where this was the case, we included the more severely affected eye and the higher dosage.

We exported the database to IBM SPSS Statistics, V.24. We analysed data using summary statistics, describing proportions. We explored continuous data for normal distribution using QQ plots; as they were not normally distributed, we used non-parametric tests for analysis throughout: median/IQR for summary statistics, the Wilcoxon signed rank tests to compare the medians of two related variables, Friedman test and Kendall’s coefficient of concordance to compare the medians of more than two related variables and the independent samples median test. To address missing data, we report the number of datasets available at each time point (figure 1). Missing data, often from lost to follow-up, were excluded from the analysis. This report follows the Standard Protocol Items: Recommendations for Interventional Trials guidance for reporting observational studies.¹¹

RESULTS

Participants

Eliminating duplicates from the electronic search output, we identified n=512 records of CYP age 18 years or younger which mentioned CsA (figure 1). After review of the individual electronic records, we excluded 27 cases, either as critical information was not included, principally the start date of treatment, or as the identified patients had not used CsA (figure 1). A total of 276 CYP had been prescribed CsA for atopic keratoconjunctivitis (n=99), blepharokeratoconjunctivitis (n=145) or other forms of acute/chronic ocular surface inflammation

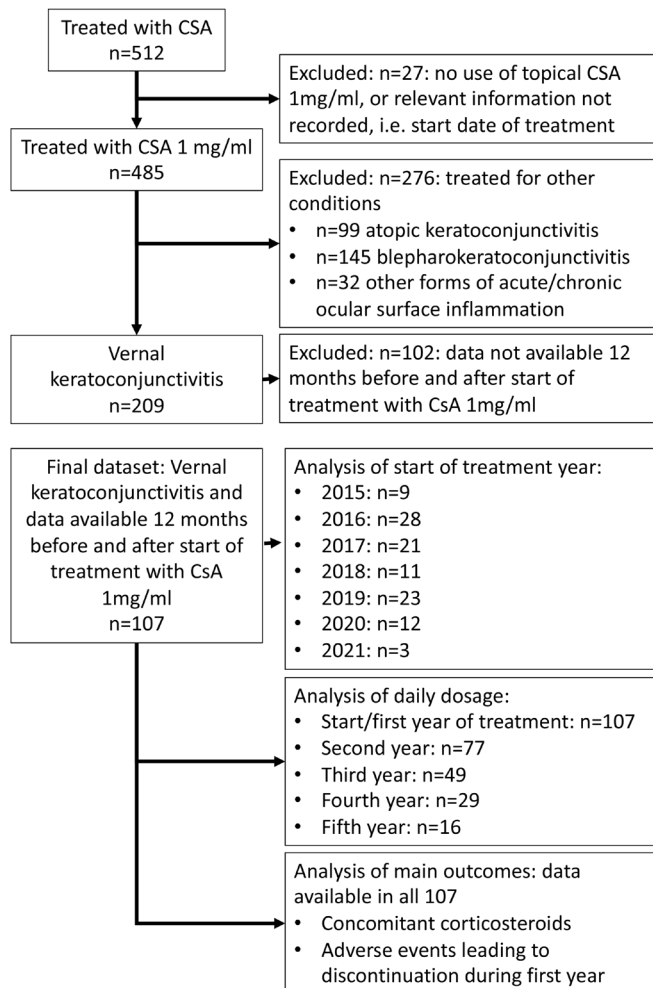


Figure 1 Identification of included records. We searched electronic patient records for children and young people (CYP) under 18 years of age treated with CsA. We excluded cases not treated with CsA 1 mg/mL, or where relevant information was missing. We also excluded those treated for inflammatory ocular surface conditions other than vernal keratoconjunctivitis. We included 107 records in the analysis for which data were available 12 months before and after the start of CsA 1 mg/mL. CsA, ciclosporin A.

(n=32), and n=209 for VKC; in n=107 of these, data were available from 12 months before to 12 months after the start of CsA, and these were included in the evaluation (figure 1).

Outcome data: numbers of outcomes, events or summary measures over time

A number of available datasets for each analysis are shown in figure 1. By calendar year, initial daily dosage data were available for n=9 CYP in 2015, 28 in 2016, 21 in 2017, 11 in 2018, 23 in 2019, 12 in 2020 and 3 in 2021 (total n=107, figure 1). Data about daily dosage of CsA 1 mg/mL were available for n=107 CYP for the first year of treatment, 77 for the second year, 49 for the third year, 29 for the fourth year and 16 for the fifth year from the first prescription (figure 1).

Safety data, that is, data about adverse events leading to temporary or permanent discontinuation of treatment, were available for all 107 cases. Data about severe corneal events due to the underlying condition were identified in the electronic records of 18 CYP.

Demographic characteristics

Seventy-eight of 107 included cases were boys (72.9%). The median age (IQR) at the start of treatment with CsA was 11.0 (8.4–12.8) years, with a range from 4.4 to 18 years. Thirty-three CYP (30.8%) were from black/black British background, 19 (17.8%) from Asian/Asian British background, 14 (13.1%) white, 3 (2.8%) mixed; 31 families (29%) selected ‘other ethnic group’ and 7 (6.5%) did not give an answer.

Indications for CsA

The main indication for commencing CsA was either an acute or uncontrolled episode of inflammation (n=80, 74.8%), or the intention to reduce long-term use of tCS (n=27, 25.2%). Of the 107 CYP in this cohort, 14 (13.1%) had documented episodes of raised IOP requiring treatment either before CsA was started or during the follow-up period.

Prescribed dosage of CsA

The median prescribed dosage at the start of treatment over the whole review period (2015–2021) was 2 (IQR 1–2) applications per day. In all reviewed years, the median dosage at start of treatment was between 1 and 2 applications per day (online supplemental figure 1). The differences between medians between years were statistically significant, with $p=0.048$ on the independent samples median test.

Median minimum and maximum prescribed daily dosage remained stable over treatment years, with a median between 1 and 2 applications per day for both. The IQR was between 1 and 2 doses/day for the minimum dosage, and between 1 and 4 doses/day for the maximum dosage. There was no statistically significant difference across years, with $p>0.05$ on Friedman Test and Kendall’s coefficient of concordance (minimum dosage $p=0.498$, maximum dosage $p=0.781$) (online supplemental figure 2).

Timing of start of treatment

The highest number of prescriptions for CsA was issued at the start of the calendar year 2016, as many CYP were switched from unlicensed CsA preparations such as veterinary CsA 0.2% eye ointment when commercial CsA 1 mg/mL (Ikervis) became available (online supplemental figure 3). In subsequent years, fewer CYP started CsA in the winter, and peak frequencies were observed in the summer months (online supplemental figure 3).

Duration of prescription and changes in daily dosage during follow-up

The median duration of treatment with CsA was 23.5 (IQR 12.0–37.8) months, ranging from discontinuation within a day to a maximum of 66.6 months.

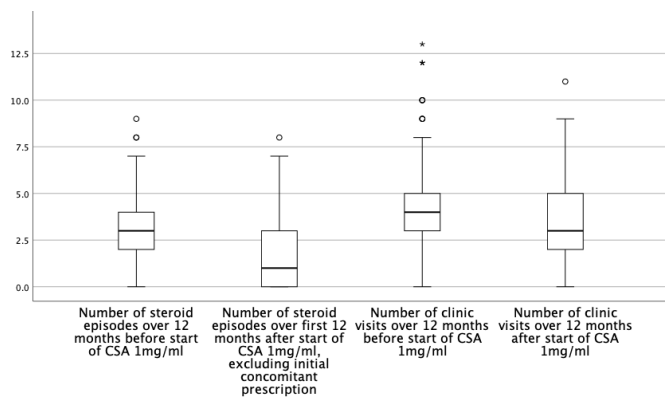


Figure 2 Left: starting CsA 1 mg/mL significantly reduced the number of prescriptions for topical corticosteroids for vernal keratoconjunctivitis, comparing the 12 months before and after start of treatment. Right: similarly, starting CSA 1 mg/mL significantly reduced the number of clinic visits. CsA, ciclosporin A.

Over the follow-up period, 59 CYP not using high-frequency CsA (three or four times a day) presented with acute inflammatory episodes requiring an increase in treatment. In n=43 of these (72.9%), the prescribed CsA dosage was then increased to three or four times a day; in the other n=16, tCS were restarted or their frequency was increased, while the frequency of CsA application was maintained.

Impact on prescription of tCS

tCS were prescribed concomitantly with the start of CsA in n=82 (76.6%). The most commonly prescribed formulation was dexamethasone 0.1% eye-drops (online supplemental table 1).

The median number of inflammatory episodes requiring treatment with tCS was 3 (IQR 2–4) in the 12 months prior to CsA, and 1 (IQR 0–3) over the 12 months after starting CsA, excluding steroid prescriptions concomitant with the first CsA prescription (figure 2). This difference was statistically significant (Wilcoxon signed ranks test, two tailed, $p < 0.01$).

Subsequent to the start of CsA, the dosage of tCS was reduced in 79 CYP (96.3% of 82). In 67 CYP (81.7% of 82), topical steroids were discontinued completely.

Impact on clinic visits

The median number of clinic visits over the 12 months before start of CsA was 4 (IQR 3–5) and after start of CsA, 3 (IQR 2–5, figure 2). This difference was statistically significant (Wilcoxon signed ranks test, two tailed, $p < 0.01$).

Adverse events and other causes for discontinuation of treatment

CsA was discontinued during the first year in 51 of 107 (47.4%) (table 1). Adverse events linked to CsA prompted discontinuation in a small number of cases: stinging (instillation site pain) in 6/107 (5.6%) and a

Table 1 Adverse events leading to temporary or permanent discontinuation of CsA 1 mg/mL during the first 12 months of treatment and other reasons to stop CsA

Reason CSA 1 mg/mL discontinued	n (total n=51)	% of whole cohort (n=107)
Adverse events		
Stinging (instillation site pain)	6	5.6
Diffuse vesiculo/papular skin rash all over body	1	0.9
Other reasons		
Hospital-issued prescription finished after 4 weeks, and not extended by family or by family doctor	26	24.3
Perception that CSA 1 mg/mL no longer needed	15	14.0
Inflammation not sufficiently controlled	1	0.9
Switched to tacrolimus 0.03%	1	0.9
Adherence problems	1	0.9
Total	51	47.7

CsA, ciclosporin A.

diffuse vesiculo-papular rash over the whole body in 1/107 (0.9%, table 1). The rash resolved rapidly after discontinuation of CsA. There were no cases of serious ocular adverse events nor of lasting systemic adverse effects. The most common reasons for discontinuing treatment were the hospital-issued prescription running out after 4 weeks, and families either not seeking a re-prescription by the family doctor, or the family doctor not issuing a repeat prescription, and a perception that CsA was no longer needed (table 1). Lack of efficacy, that is, insufficient control of the ocular surface inflammation, led to discontinuation in 1/107 (0.9%, table 1). In 31/51 cases (60.8%), CsA was restarted.

Over the entire observation period, CsA was discontinued by 72 CYP (67.3% of 107). The decision to stop was in most cases made by the family (n=53, 49.5% of 107). The treating clinician recommended discontinuation in n=21 (19.6% of 107), with some overlap between the two groups.

Severe corneal episodes and prior use of CsA

Eighteen CYP developed at least one severe corneal event related to VKC. Ten had one severe episode, five had two severe, two had four severe and one had five severe events. The median (IQR) age at the first severe episode was 8.4 (6.8–10.8) years. Of the combined 34 severe episodes, 28 (82.4%) were shield/plaque ulcers (stage 3 corneal epithelial disease¹³), 5 (14.7%) were epithelial defects/macroerosions/ulcers with clear or translucent base or with minimal plaque (stage 2) and 1 (2.9%) was coarse epitheliopathy (stage 1). In 47% of these events (n=16), CYP were not using any CsA at the time of presentation.

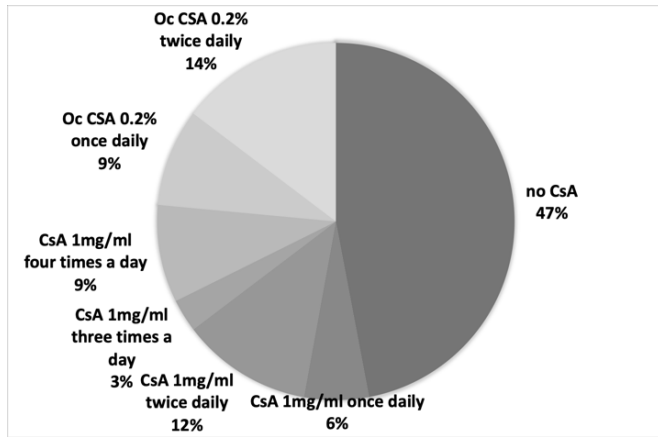


Figure 3 Nearly half of children and young people presenting with severe corneal epithelial events were not using any CsA at the time of presentation; just under a quarter were using a veterinary off-label preparation (Oc CsA 0.2%), and the remaining quarter were using G CsA 1 mg/mL between one and four times a day. Chart shows percentage of total number of events (n=34). CsA, ciclosporin A.

Just under a quarter were using a veterinary off-label preparation (Oc CsA 0.2%), and the remaining quarter were using G CsA 1 mg/mL between one and four times a day (figure 3).

DISCUSSION

This study provides information about the steroid-sparing effect of CsA 1 mg/mL in VKC and a potential reduction of hospital visits with improved long-term control of inflammation. In our series, even with mostly only twice daily administration, CsA 1 mg/mL significantly reduced the number of hospital visits and episodes of acute ocular surface inflammation requiring tCS. In over 80% of CYP, tCS could be discontinued during the first year after starting CsA. The incidence of adverse events leading to temporary or permanent discontinuation of CsA was low (stinging/instillation site pain 5.6%, skin rash 0.9%). The most common reasons for stopping CsA were a perception that the inflammation had resolved, or the hospital-initiated prescription not being continued by the family or by the family doctor. In around 60% of CYP who stopped CsA, it was restarted by the hospital specialist. Lastly, we observed that nearly half of severe corneal events occurred in CYP who had not been using CsA in the weeks leading up to presentation.

This work has limitations inherent in the study design. Lack of a control group may create selection bias, which we tried to mitigate by including all consecutive CYP who met inclusion criteria. Misclassification of diagnosis may be another limitation. In routine clinical practice, we do not use clinical trial-level severity grading systems, and involvement of multiple specialists can lead to variation in diagnosis. However, all clinicians at our institution apply the same diagnostic criteria, and these are based on expert opinion and peer-reviewed publications, with local guidelines based on these.^{1 8 9} The most likely

misclassification is between VKC and AKC, as signs of ocular surface allergy may precede the development of lid margin changes or atopic dermatitis. We sought to mitigate this possibility by allowing a change in diagnosis from VKC to AKC, if the CYP developed features at a later stage. In future work, it would be desirable to establish a molecular diagnosis based on cytokine profiles, recognising that VKC is a Th2CD4⁺T cell-driven response, whereas AKC is predominantly Th1 mediated.^{1 8 13 14} While CsA is effective in both conditions, in this work we focus on its on-label indication, that is, severe VKC.

We identified gaps in the documentation of IOP data in clinical practice. We had intended to use the recommended definition elevation of 10 mm Hg or more from baseline.² However, this was not possible, as clinicians did not systematically record IOP at initial presentation. Our finding that nearly 13% of CYP experienced steroid-induced ocular hypertension is therefore an estimate only. For future work, we recommend clear documentation of IOP at every visit.¹⁵ Few published data on the steroid-sparing effect of the commercial formulations of CsA 1 mg/mL in paediatric VKC are available for direct comparison. We used measures previously described for tacrolimus, where tCS could be discontinued or tapered in 10 of 10 patients with steroid-refractory ocular surface inflammation, including one case of VKC,¹⁶ and also in two case series of 18 VKC patients, 60% of whom could discontinue tCS after 1 month of CsA 2% treatment, or after 2 months of CsA 0.05%.^{17 18} We were able to discontinue tCS treatment in over 80%. This is higher than the figure of 50% we previously reported across a variety of ocular surface inflammatory conditions,¹⁹ probably due to a longer observation period of 12 months in the present work.

An alternative method to quantify the steroid-sparing effect of immunomodulators is a scoring system which aims to take into account the ‘potency’ of different types of tCS.^{19 20} However, these ‘potency scores’ tend to reflect transcorneal penetrance, relevant in the management of uveitis, not ocular surface inflammation.² In addition, scoring systems do not include ‘safer’ tCS such as rimexolone and loteprednol,² and do not take into account the interindividual variability in the IOP-response to tCS.²⁰

The VEKTIS trial of CsA for VKC reported the use of topical dexamethasone 0.1% four times a day for up to 5 days as ‘rescue medication’; 70% of participants on twice daily CsA did not require rescue during the first 4 months, and over 89% did not require any between months 4 and 10 from baseline.^{3 4} In the last 2 of the 12 months, the need for tCS increased, probably due to the ‘new allergy season’ starting; even then, over 80% of CYP did not require tCS.⁴ CYP who used CsA only intermittently were nearly three times more likely to require tCS rescue medication than those who were using it continuously.⁴ In our study, we observed that tCS could be discontinued in 82% of CYP over 12 months after starting CsA, which is similar to the figures reported in the VEKTIS trial.

We did not review the use of oral corticosteroids, as we would only use these for severe corneal episodes.¹² We also do not report the use of concomitant medication other than tCS; in our practice, all CYP receive a dual-acting antihistamine/mast cell inhibitor as well as CsA.²¹

The number of hospital clinic attendances before and after using CsA is a soft marker of inflammation control, as multiple factors affect bookings in daily practice. However, as patients have access to same-day appointments in our children's eye emergency clinic, it is likely that the slight reduction in visits after starting CsA is a real effect.

Recurrence after discontinuation of CsA was a common occurrence in our cohort, and in 60% CsA was re-started. This is in line with previous reports that CsA may have a prophylactic effect on flare-ups or reduce their severity.^{5,22} Continuous treatment may be beneficial, even for those who display the typical 'seasonal' pattern of exacerbations.²³

The optimum dosage of CsA 1mg/mL throughout the year remains an open question. The VEKTIS trial reported slightly greater efficacy with four times versus twice daily use.^{3,4} Contrary to our expectations, local prescribing habits did not change after VEKTIS, and the most commonly prescribed dosage remained twice daily, probably because we used compounded preparations of CsA in the past, for which the recommended dosage was once or twice daily. However, we did note that in 73% of those who suffered acute exacerbations and were not already using CsA at higher dosage (three or four times a day), the daily dosage was then increased. As VKC is a chronic condition, and families tend to be familiar with the CYP's 'pattern', it may be advisable to recommend that they should continue using CsA at low frequency throughout the year and to increase dosage to high-frequency when the inflammation begins to flare up. As family doctors in the community can extend the prescription once it has been initiated by a hospital specialist, the triangle of specialist—general practitioner—parent/carer working together can optimise VKC management. It is important for hospital specialists to explain, both to families and to the family practitioner, that the initial prescription of CsA will not cure VKC, and that ongoing treatment is required to reduce the risk of recurrences.^{5,24}

In our cohort, we encountered one case of skin rash immediately after the start of CsA which affected the whole body and resolved with no lasting harm when CsA was discontinued. While none of the 169 VEKTIS participants displayed a skin rash, this has previously been reported in a case series of 32 CYP receiving CsA 2%.²⁵

Our findings are likely to be generalisable to other settings. Our facility serves a population of diverse ethnic origin, and our patients share the age and ethnic profile typical for VKC.¹

This study confirms the real-world efficacy and excellent safety profile of topical ciclosporine A in reducing the need for tCS and hospital visits in CYP with VKC. Excellent communication between hospital practitioners

and parents/carers and general practitioners is needed to ensure ongoing supply of medication and to reduce the risk of flare-ups.

Acknowledgements The work was carried out at the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology.

Collaborators n/a.

Contributors AHD-N, MH, KM and CR designed the study. AHD-N ran the search of electronic records, extracted and summarised data and wrote the first draft of the manuscript. MH, KM, CR and VC reviewed the manuscript and contributed to the final version. AHD-N is the guarantor for the content of this article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests AHD-N has received payment from Santen for lectures, travel and advisory boards, and VC has received payment for facilitating and running an educational event.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Moorfields Eye Hospital National Health Service (NHS) Foundation Trust approved this work as audit/service evaluation (registration number 860). External ethical review was not required for this study. It adhered to the tenets of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Annegret Hella Dahlmann-Noor <http://orcid.org/0000-0002-7402-4350>

REFERENCES

- Leonardi A, Bogacka E, Fauquet JL, et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy* 2012;67:1327–37.
- Musleh MG, Bokre D, Dahlmann-Noor AH. Risk of intraocular pressure elevation after topical steroids in children and adults: a systematic review. *Eur J Ophthalmol* 2020;30:856–66.
- Leonardi A, Doan S, Amrane M, et al. A randomized, controlled trial of cyclosporine a cationic emulsion in pediatric vernal keratoconjunctivitis: the VEKTIS study. *Ophthalmology* 2019;126:671–81.
- Bremond-Gignac D, Doan S, Amrane M, et al. Twelve-Month results of cyclosporine a cationic emulsion in a randomized study in patients with pediatric vernal keratoconjunctivitis. *Am J Ophthalmol* 2020;212:116–26.
- Feizi S, Javadi MA, Alemzadeh-Ansari M, et al. Management of corneal complications in vernal keratoconjunctivitis: a review. *Ocul Surf* 2021;19:282–9.
- Roumeau I, Coutu A, Navel V, et al. Efficacy of medical treatments for vernal keratoconjunctivitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2021;148:822–34.

- 7 Rasmussen MLR, Schou MG, Bach-Holm D. Comparative efficacy of medical treatments for vernal keratoconjunctivitis in children and young adults: a systematic review with network meta-analyses. *Acta Ophthalmologica* 2021.
- 8 Leonardi A. Allergy and allergic mediators in tears. *Exp Eye Res* 2013;117:106–17.
- 9 Sacchetti M, Abicca I, Bruscolini A, et al. Allergic conjunctivitis: current concepts on pathogenesis and management. *J Biol Regul Homeost Agents* 2018;32:49–60 <https://pubmed.ncbi.nlm.nih.gov/29552874/>
- 10 Daniel MC, O’Gallagher M, Hingorani M, et al. Challenges in the management of pediatric blepharokeratoconjunctivitis / ocular rosacea. *Expert Rev Ophthalmol* 2016;11:299–309.
- 11 von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573–7.
- 12 Fernando P, Marziali E, Chlubek M, et al. Pulsed oral corticosteroids for the treatment of vernal and atopic keratoconjunctivitis: a management plan. *Eye* 2021;35:1277–8.
- 13 Metz DP, Hingorani M, Calder VL, et al. T-Cell cytokines in chronic allergic eye disease. *J Allergy Clin Immunol* 1997;100:817–24.
- 14 Calder VL, Jolly G, Hingorani M, et al. Cytokine production and mRNA expression by conjunctival T-cell lines in chronic allergic eye disease. *Clin Exp Allergy* 1999;29:1214–22.
- 15 Dahlmann-Noor AH, Puertas R, Tabasa-Lim S, et al. Comparison of handheld rebound tonometry with Goldmann applanation tonometry in children with glaucoma: a cohort study. *BMJ Open* 2013;3. doi:10.1136/bmjopen-2012-001788. [Epub ahead of print: 02 04 2013].
- 16 Miyazaki D, Tominaga T, Kakimaru-Hasegawa A, et al. Therapeutic effects of tacrolimus ointment for refractory ocular surface inflammatory diseases. *Ophthalmology* 2008;115:988–92.
- 17 Doan S, Gabison E, Abitbol O, et al. Efficacité de la ciclosporine A en collyre à 2 % en tant qu’épargneur de corticoïdes dans le traitement de la kératoconjunctivite vernale corticodépendante. *Journal Français d’Ophthalmologie* 2007;30:697–701.
- 18 Chatterjee A, Bandyopadhyay S, Kumar Bandyopadhyay S. Efficacy, Safety and Steroid-sparing Effect of Topical Cyclosporine A 0.05% for Vernal Keratoconjunctivitis in Indian Children. *J Ophthalmic Vis Res* 2019;14:412–418.
- 19 Hingorani M, Moodaley L, Calder VL, et al. A randomized, placebo-controlled trial of topical cyclosporin A in steroid-dependent atopic keratoconjunctivitis. *Ophthalmology* 1998;105:1715–20.
- 20 Fini ME, Schwartz SG, Gao X, et al. Steroid-Induced ocular hypertension/glaucoma: focus on pharmacogenomics and implications for precision medicine. *Prog Retin Eye Res* 2017;56:58–83.
- 21 Ghauri A-J, Biswas S, Manzouri B, et al. Management of vernal keratoconjunctivitis in children in the United Kingdom: a review of the literature and current best practice across six large United Kingdom centers. *J Pediatr Ophthalmol Strabismus* 2022:1–12.
- 22 Lambiase A, Leonardi A, Sacchetti M, et al. Topical cyclosporine prevents seasonal recurrences of vernal keratoconjunctivitis in a randomized, double-masked, controlled 2-year study. *J Allergy Clin Immunol* 2011;128:896–7.
- 23 Bonini S, Bonini S, Lambiase A, et al. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup. *Ophthalmology* 2000;107:1157–63.
- 24 Kim SE, Nowak V, Quartilho A. Systemic interventions for severe atopic and vernal keratoconjunctivitis in children and young people up to the age of 16 years. *Cochrane Database of Systematic Reviews* 2020.
- 25 Doan S, Duong MH, Hoang-Xuan T. Efficacy and Safety of Topical 2% Cyclosporine in Steroid-Dependent Childhood Ocular Surface Diseases. *Ocul Surf* 2005;3:S57.