Original Article

Taiwan J Ophthalmol 2023;13: 68-74

Supplementary material available online

Access this article online

Quick Response Code:

Website: www.e-tjo.org

DOI: 10.4103/tjo.TJO-D-22-00140

Efficacy and safety of topical cyclosporine 0.1% in moderate-to-severe dry eye disease refractory to topical cyclosporine 0.05% regimen

Yuan-Hsi Chan[1], Chi-Chin Sun[1,2]*

Abstract:

PURPOSE: To evaluate the efficacy and safety of 0.1% cyclosporine A cationic emulsion (CsA CE) following prior treatment with 0.05% cyclosporine A anionic emulsion (CsA AE) in moderate to severe dry eye disease (DED).

MATERIALS AND METHODS: We retrospectively identified patients with moderate-to-severe DED who had shown an inadequate response to twice-daily use of topical 0.05% CsA AE but showed a significant improvement after switching to 0.1% CsA CE daily. Dry eye parameters before and after CsA CE were evaluated by tear break-up time (TBUT), corneal fluorescein staining (CFS), cornea sensitivity, Schirmer's test without anesthetics, and Ocular Surface Disease Index questionnaire.

RESULTS: Twenty-three patients, including ten patients with Sjogren syndrome and five patients with rheumatoid arthritis, were reviewed. After a 2-month course of treatment with topical 0.1% CsA CE, significant improvements were noted for CFS ($P < 0.001$), corneal sensitivity ($P = 0.008$), and TBUT ($P = 0.01$). Efficacy was similar in the autoimmune versus nonautoimmune group. 39.1% of patients reported treatment-related adverse events, while the majority was transient instillation pain. Visual acuity and intraocular pressure had no significant changes during the study.

CONCLUSION: In patients with moderate to severe DED refractory to 0.05% cyclosporine, shifting to 0.1% cyclosporine showed improvement in objective signs but with lower treatment tolerability in the short term.

Keywords:

Cyclosporine, dry eye syndromes, tears

Introduction

Dry eye disease (DED) is an extremely common ocular surface disorder with variable prevalence due to differences in definition and classification. Female and the elderly population have reported to have a higher prevalence.[1,2] With an aging population and increase in digital device usage, visual disturbance, and discomfort associated with DED is expected to grow.[1] The pathogenesis is believed to be multifactorial, with the combination of tear film instability, ocular surface inflammation, ocular surface damage, and neurosensory abnormalities.[3,4] Anti-inflammatory regimens focused on breaking the self-perpetuating inflammatory cycle are commonly used for moderate-to-severe disease which tears film replacement alone may not be sufficient.[5] These therapies include topical steroids, cyclosporine A (CsA) or lifitegrast (Xiidra, Novartis, US). Compared to steroid, CsA does not

[1]Department of Ophthalmology, Chang Gung Memorial Hospital, Keelung, Taiwan, [2]School of Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan

***Address for correspondence:**
Dr. Chi-Chin Sun, No. 222, Maijin Road, Anle District, Keelung City 204, Taiwan.
E-mail: arvin.sun@msa.hinet.net

Submission: 16-10-2022
Accepted: 21-12-2022
Published: 13-03-2023

How to cite this article: Chan YH, Sun CC. Efficacy and safety of topical cyclosporine 0.1% in moderate-to-severe dry eye disease refractory to topical cyclosporine 0.05% regimen. Taiwan J Ophthalmol 2023;13:68-74.

induce cataract formation or increase intraocular pressure,[6] thus, it is a safer long-term pharmacologic therapy for the inflammatory ocular surface disease.[7] A cationic oil in water emulsion of 0.1% CsA cationic emulsion (CsA CE) (Ikervis, Santen)[8] was designed to increase the residence time of CsA on the cornea through the interaction of cationic surfactants and the negatively charged mucin in the tear film.[8-11] Notably, cationic emulsion droplet showed clinical benefits for DED.[12] Two phase 3 randomized control trials (SANSIKA and SICCANOVE)[13,14] and their pooled analysis[15] have established that CsA CE produced significant improvement in both symptoms and signs compared to its vehicle in moderate-to-severe DED.

A Compassionate Use Programme in French[16] was conducted and showed that in DED patients with moderate-to-severe keratitis, the majority of patients who had previously received anionic or compound CsA experienced an improvement in both symptoms and sign with CsA CE. However, previous studies did not investigate the use of daily 0.1% CsA CE when patients did not respond favorably with a 0.05% anionic emulsion CsA anionic emulsion (CsA AE) (Restasis, Allergan)[17] dosed twice daily. Furthermore, prior studies were also conducted on the Caucasian population and the finding in the Asian population is unknown. This study aims to evaluate the efficacy and safety of 0.1% CsA CE refractory to 0.05% CsA AE in patients with moderate-to-severe dry eye.

Materials and Methods

Case selection and study design

This is a retrospective case series of consecutive DED patients followed at a single institution (Chang Gung Memorial Hospital, Keelung, Taiwan). Twenty-three patients, including ten patients with Sjogren syndrome and five patientswith rheumatoid arthritis, were reviewed. Chart review was approved and a waiver of written informed consent was granted by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan (No.: 202000799B0). Of note, informed consent was obtained from the representative case to publish the images in an online open-access publication. All methods were performed in accordance with the declaration of Helsinki.

We included patients with moderate to severe DED (Corneal Fluorescein staining [CFS] score of 3, 4, or 5 by the modified Oxford scale[18]) who had an inadequate response to twice daily use of 0.05% CsA AE. All of the patients were 18 and older, and received artificial tears and 0.05% CsA AE as the mainstay treatment for DED for more than 3 months. Concomitant use of steroids was either 0.1% fluorometholone three times a day, 0.1% betamethasone drops three times a day, or absent. All patients included in the study were shifted to a 2-month treatment with daily 0.1% CsA CE and were then shifted back to twice daily 0.05% CsA AE.

The time point of shifting to CsA CE treatment was established as the baseline, 2 months after CsA CE administration as visit 1 and the first clinic visit after shifting back to CsA AE as visit 2. Dry eye parameters at each time point were analyzed and compared between the two medications. Efficacy analysis was performed in the worst eligible eye, which was defined as the higher CFS at the baseline visit. Treatment-related adverse effects were also documented.

Patients with a history of ocular trauma, infection, inflammation other than DED within 3 months of the study, or with other ocular conditions other than DED requiring topical ocular treatment during the study, or contact lens wearer were excluded. Patients who required topical medication adjustment other than CsA during the study and patients who discontinued 0.1% CsA CE before visit 1 were excluded from the efficacy analysis.

Data collection

Data extraction included demographic details, disease profile, ocular examination record, concomitant medication use, treatment-related adverse effect, and dry eye-related subjective/objective parameter.

Methods of assessment for each dry eye parameters as followings

Corneal fluorescein staining

After the ocular surface was stained with fluorescein paper, external eye photo was taken with a biomicroscopy image system. The CFS grading would be scored according to the modified Oxford grading scale.

Fluorescein tear break up time

To measure tear break-up time (TBUT), fluorescein was instilled into the patient's tear film and the patient was asked not to blink while the tear film was observed under a broad beam of cobalt blue illumination. The number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film was recorded by a single clinician (Sun C-C).

Schirmer's test

A filter paper was placed in the lower fornix of the patient without instillation of anesthesia; the filter paper was then removed 5 min later.

Cornea sensitivity

Cornea sensitivity would be assessed with Cochet–Bonnet esthesiometer by a well-experienced technician.

Ocular surface disease index questionnaire

The patient was asked to complete the ocular surface disease index questionnaire (OSDI) questionnaire which was assisted by a well-experienced clinician.

All of the above parameters are routine examinations recorded at each visit for all dry eye patients at our clinic.

Statistical analysis

All parameters (Schirmer's test score, TBUT, cornea sensitivity, cornea fluorescein score, and OSDI questionnaire) were expressed with mean and standard deviation. To compare demographic data between groups, we analyzed quantitative data through an independent sample *t*-test and qualitative data through Chi-square test. The Kolmogorov–Smirnov normality test was performed to examine normality distribution for quantitative data. All of the quantitative variables are normally distributed. Visual acuity and intraocular pressure change after CsA CE were analyzed by paired *t*-test. Through generalized equation estimation (GEE), we first tested whether different medications (which were different in each visit) and covariates were related to the dry eye parameters change (Model 1). Age, CsA AE usage duration before the CsA CE shifting, underlying autoimmune disease, and concurrent use of topical steroid (fluorometholone as low potency steroid and betamethasone as high potency steroid) was considering as covariates. Next, Model 2 added a visit and autoimmune interaction term to evaluate whether the efficacy of each visit was comparable for autoimmune and nonautoimmune groups. A $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed with SPSS software, version 25.0 (SPSS, Inc, Chicago, IL, USA).

Results

Patient demographics

Twenty-seven patients (25 females and 2 males) were identified initially according to the inclusion and exclusion criteria, four of them were excluded from efficacy analysis due to discontinuation of 0.1% CsA CE before visit 1 (three complaint instillation pain and one complaint of sticky sensation). Other 23 patients (22 females and 1 male) were reviewed. The mean age was 61.6 ± 10.1-year-old. The baseline CFS was 3.96 ± 0.82, compatible with a definition of moderate-to-severe DED.[18] Overall, the patients had received CsA AE for a mean of 35.8 ± 24.1 months before CsA CE shifting. Among all, 15 (65.2%) received 0.1% fluorometholone drops three times a day, and five (21.7%) received 0.1% betamethasone drops three times a day as adjunctive therapy for DED before the baseline visit. No patient experienced steroid discontinuation or dosage shifting during the study. The other three (13%) did not receive steroid drops. The baseline demographics of all patients are shown in Table 1.

The autoimmune group was defined as those patients with Sjögren's syndrome or rheumatoid arthritis. Ten patients (43.5%) have Sjögren's syndrome and five patients (21.7%) have rheumatoid arthritis. While the autoimmune group had a mean age of 61.1 ± 10-year-old and a mean CFS score of 4.2 ± 0.77, those without autoimmune had a mean age of 62.6 ± 11-year-old and a mean CFS score of 3.5 ± 0.76. The baseline CFS score was higher in the former group, though not reaching statistically significant ($P = 0.05$). A comparison of baseline demographics of subgroup is shown in Table 2.

Efficacy analysis

To evaluate the efficacy of CsA CE following inadequate response with Cs AE, GEE with covariates was performed to compare dry eye parameters of each visit. After adjusting for Age, CsA AE usage duration before CsA CE shifting, underlying autoimmune disease, and concurrent use of topical steroids at baseline, estimated marginal mean is shown in Figure 1. CFS was 3.51 ± 0.56 at baseline, 2.81 ± 0.7 at visit 1, and 3.33 ± 0.61 at visit 2, which showed significantly improved after CsA CE but aggravated after discontinuation; cornea sensitivity was 4.76 ± 0.45 mm at baseline, 5.39 ± 0.36 mm at visit 1, and 5.02 ± 0.4 mm at visit 2, which showed a similar trend as CFS; TBUT was 0.91 ± 0.72 s at baseline, 1.61 ± 0.75 s at visit 1, and 1.70 ± 0.83 s at visit 2, which showed a significantly improve at visit 1 and continuous improvement after discontinuation; no significant change was noted in OSDI score (not shown in the figure) and Schirmer's test score during the study. A representative case is shown in Figure 2.

Table 1: Baseline demographic data of participants

	Participants (*n*=23)
Sex, *n* (%)	
Female	22 (95.7)
Male	1 (4.3)
Concurrent steroid (*n*)	
None	3
Fluorometholone	15
Betamethasone	5
Autoimmune disease (*n*)	
Sjögren's syndrome	10
Rheumatoid arthritis	5
None	8
Age (years)	61.6±10.1
CsA AE duration (m)	35.8±24.1
CFS	3.96±0.82
TBUT (sec)	2.00±1.20
OSDI	44.7±23.5
Cornea sensitivity (mm)	4.85±1.58
Schirmer's test (mm/5 min)	2.52±3.29

CsA AE=0.05% cyclosporine A anionic emulsion, CFS=Cornea fluorescein stain, OSDI=Ocular surface disease index, TBUT=Tear break-up time

Table 3 shows model 1 predicting each dry eye parameters through GEE with covariates adjusted (effects of covariates are not shown in Table 3, see Table S1-S5 for more information). In the most basic GEE model (Model 1), compared with baseline, visit 1 showed significant improvement in CFS (B = −0.696, 95% confidence interval (CI) [−1.046,-0.346], $P < 0.001$), TBUT (B = 0.696, 95% CI [0.164, 1.227], $P = 0.01$), and cornea sensitivity (B = 0.630, 95% CI [0.167, 1.094], $P = 0.008$) after covariates were controlled. Neither improvement nor deterioration was noted in OSDI score and Schirmer's test ($P = 0.653$ and $P = 0.353$, respectively). Notably, in Model 1, continuous improvement in TBUT after discontinuation of CsA CE was noted (B = 0.783, 95% CI [0.317, 1.249], $P = 0.001$).

To further evaluate the parameters after CsA CE discontinuation, visit 2 was compared with visit 1 (not shown in the table). In the basic model, deterioration after CsA CE discontinuation was noted in CFS (B = −0.516, 95% CI [−0.839, −0.139], $P = 0.002$) and cornea sensitivity (B = 0.373, 95% CI [0.031, 0.714], $P = 0.033$). On the other hand, neither aggravated nor continuous improvement was noted in OSDI and Schirmer's score.

To evaluate the difference in CsA CE between autoimmune and nonautoimmune group, we estimated a simple model in which dry eye parameters was predicated from the different medication (Visit), the autoimmune disease, and their interaction (Model 2). When this model was expanded to Model 2, a nonsignificant interaction in all parameters [Table 4] indicated that there was no efficacy difference between autoimmune patient and nonautoimmune patient.

For covariates analysis, aging was found to be positively correlated with CFS (B = 0.09, 95% CI [0.007, 0.174], $P = 0.033$) [Table S1] and negatively correlated with OSDI score (B = −1.53, 95% CI [−2.386, −0.673], $P < 0.001$) [Table S4]. Moreover, CsA AE usage duration before CsA CE shift was found to be negatively correlated with TBUT (B =−0.038, 95% CI [−0.068, −0.007], $P = 0.017$) [Table S2] and positively correlated with OSDI score (B = 0.429, 95% CI [0.06, 0.798], $P = 0.023$) [Table S4].

Safety analysis

Newly developed treatments related adverse events were reported in eleven of 27 patients (40.1%), while four (14.8%) discontinued due to intolerance. The most commonly reported adverse effect was instillation pain, which was reported in eight patients (29.6%). The majority

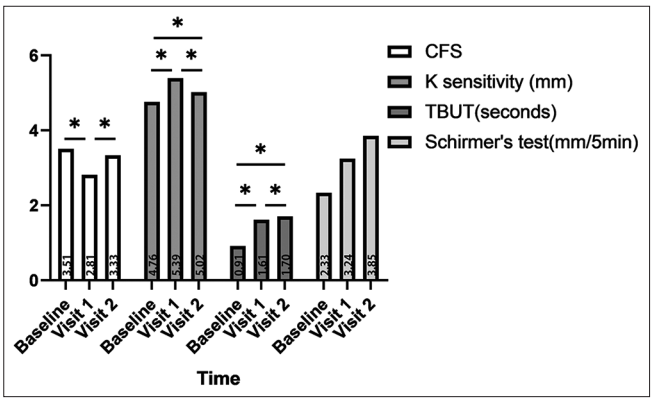

Figure 1: Graph represents change in each dry eye parameters from baseline to visit 1 and visit 2. *P < 0.05. CFS: cornea fluorescein stain, TBUT: tear break up time

Table 2: Comparison of demographics between autoimmune and nonautoimmune (quantitative data via independent sample *t*-test and qualitative data via Chi-square test)

	Autoimmune (*n*=15)	None (*n*=8)	*P*
Sex, *n* (%)			0.161
Female	15 (100)	7 (87.5)	
Male	0	1 (12.5)	
Concurrent steroid (*n*)			0.399
None	1	2	
Fluorometholone	10	5	
Betamethasone	4	1	
Age (years)	61.1±10.0	62.6±11.0	0.734
CsA AE duration (m)	37.5±25.2	32.6±23.2	0.653
CFS	4.2±0.77	3.5±0.76	0.050
TBUT (s)	1.73±1.16	2.5±1.07	0.137
OSDI	44.79±24.6	44.56±23.06	0.983
Cornea sensitivity (mm)	4.93±1.56	4.69±1.73	0.732
Schirmer's test (mm/5 min)	1.6±1.55	4.25±4.89	0.064

CsA AE=0.05% cyclosporine A anionic emulsion, CFS=Cornea fluorescein stain, OSDI=Ocular surface disease index, TBUT=Tear break-up time

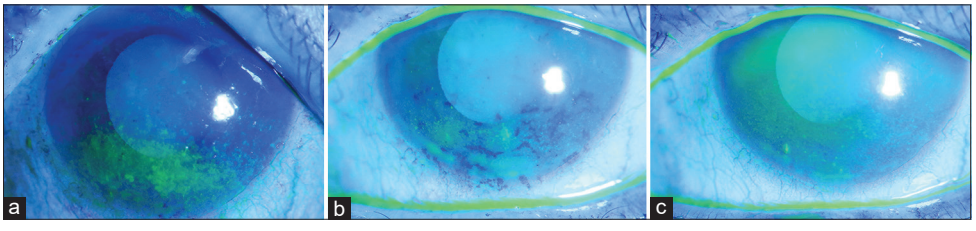

Figure 2: External eye photography of a 54-year-old woman with Rheumatic arthritis (a). Initial cornea fluorescein stain score showed 5 at baseline in her left eye, (b). after 2 months of 0.1% cyclosporine cationic emulsion, cornea stain improved, and (c). after discontinuation of 0.1% cyclosporine cationic emulsion, cornea stain aggravated again

Table 3: Results from generalized estimate equation predicting each dry eye parameters (model 1)

Model 1†	*B*	95% CI	*P*
CFS score			
Visit			
2	−0.180	−0.429-0.069	0.156
1	−0.696	−1.046-0.346	<0.001*
Baseline	Reference		
TBUT			
Visit			
2	0.783	0.317-1.249	0.001*
1	0.696	0.164-1.227	0.01*
Baseline	Reference		
Cornea sensitivity			
Visit			
2	0.258	0.011-0.505	0.041*
1	0.630	0.167-1.094	0.008*
Baseline	Reference		
OSDI			
Visit			
2	−2.035	−6.968-2.898	0.419
1	1.135	−3.813-6.083	0.653
Baseline	Reference		
Schirmer's test score			
Visit			
2	1.528	−1.070-4.127	0.249
1	0.913	−1.015-2.841	0.353
Baseline	Reference		

*P<0.05, †Effect of covariates were not shown in the table. CsA AE=0.05% cyclosporine A anionic emulsion, CI=Confidence interval, TBUT=Tear break-up time, CFS=Cornea fluorescein stain, OSDI=Ocular surface disease index

Table 4: Results from generalized estimate equation predicting each dry eye parameters (model 2)

Model 2†	*B*	95% CI	*P*
CFS score			
Visit 2× autoimmune	−0.031	−0.603-0.541	0.916
Visit 1× autoimmune	−0.083	−0.697-0.864	0.834
TBUT			
Visit 2× autoimmune	−0.717	−1.651-0.218	0.133
Visit 1× autoimmune	−0.658	−1.744-0.427	0.235
Cornea sensitivity			
Visit 2× autoimmune	−0.105	−0.665-0.454	0.712
Visit 1× autoimmune	−0.471	−1.587-0.646	0.409
OSDI			
Visit 2× autoimmune	1.546	−10.515-13.608	0.802
Visit 1× autoimmune	−0.215	−9.787-9.357	0.965
Schirmer's test			
Visit 2× autoimmune	0.088	−6.012-6.188	0.978
Visit 1× autoimmune	−0.325	−4.941-4.201	0.890

†Effect of covariates was not shown in the table. OSDI=Ocular surface disease index, TBUT=Tear break-up time, CFS=Cornea fluorescein stain, CI=Confidence interval

of instillation pain was mild and transient (<15 min). Two patients (7.4%) reported tearing, two patients (7.4%) reported eye irritation, one patient (3.7%) reported eye redness and one patient (3.7%) reported pruritus. There was no treatment-related serious adverse events noted throughout the study. Moreover, during the study, there was no significant change in visual acuity and intraocular pressure [Table 5].

Discussion

Our study demonstrates a significant improvement in objective signs when shifting from 0.05% CsA AE to 0.1% CsA CE in patients with moderate-to-severe dry eye.

In daily practice, many patients experienced refractory dry eye symptoms and keratitis despite long-term use of 0.05% CsA AE. The efficacy of 0.1% CsA CE in moderate-to-severe dry eye patients had been well established while comparing to its vehicle.[13,14] Moreover, in an *in vitro* dry eye model, CsA CE had more potent anti-inflammatory and antiapoptotic effects while compared to CsA AE.[19] A previous study had compared CsA dose ranging from 0.05%, 0.1%, 0.2%, or 0.4% and found that 0.1% gave the most consistent objective improvement.[20] However, whether shifting from 0.05% CsA AE to 0.1% CsA CE provides further treatment benefit is unclear.

First, we reported a significantly increase in TBUT for CsA CE following treatment, and with an observed continuous effect even after discontinuation. The effect might be related to both CsA and cationic emulsion. Treatment benefit of CsA included improvement in TBUT, corneal and conjunctiva staining, and Schirmer's test.[21] Cationic emulsions further mimic a healthy tear film by increasing water retention, replenishing the lipid layer, modulating tear film osmolality, stabilizing tear film, and blocking inflammation.[22]

We also found a statically significant improvement in CFS after 2 months of 0.1% CsA CE shift. Our finding is consistent with the French early-access program, 16 which showed that the majority of patients do experience an improvement in clinical sign with 0.1% CsA CE after inadequate treatment with 0.05% CsA AE.

On the other hand, persistent CFS was observed after 0.1% CsA CE discontinuation in our study, which was different from the extension study of SANSIKA.[23] They demonstrated that majority of patients did not experience a deterioration after CsA CE discontinuation. We believed that it could be partially explained by the relatively short duration of CsA CE administered in our patients, which may not have sufficient time to achieve a CFS score ≦2 as in the 2-year post-SANSIKA extension study.

Ocular surface sensitivity has been considered a vital biomarker in DED.[24] Cornea innervation plays an important role in maintaining a healthy

Table 5: Comparison of visual acuity and intraocular pressure between visit (via paired *t*-test)

	Baseline	Visit 1	*P*
Visual Acuity, OD (logMAR)	0.41	0.42	0.769
Visual Acuity, OS (logMAR)	0.35	0.38	0.602
IOP OD (mmHg)	13.2	13.9	0.202
IOP OS (mmHg)	13.8	14.2	0.455

IOP=Intraocular pressure, OD=Oculus dexter, right eye OS=Oculus Sinister, left eye logMAR=Logarithm of the minimum angle of resolution

corneal microenvironment,[25,26] by the combination of nerve-derived trophic factors, neural regulation of tear production and blinking, and evoking mucous secretion.[27] Decreased density of cornea innervation had been established in both Sjögren's syndrome-related DED[28] and nonSjögren DED.[29] Our results revealed significantly increased corneal sensitivity following CsA CE treatment, which was consistent with a previous study by Toker and Asfuroğlu.[30] Furthermore, deterioration after discontinuation was also observed. Several mechanisms had been postulated regarding CsA on nerve regeneration. CsA has a neurotrophic effect either by directly acting on nerve cells[31] or by inducing the epithelial cell to secret nerve growth factor.[32] Furthermore, as the primary mode of action, CsA breaks the vicious cycle of dry eye by reducing inflammation and may re establish a healthy environment for nerve regeneration.[33]

Improvement failed to reach statistical significance in Schirmer's test and OSDI score. The absence of significance in the subjective OSDI questionnaire could be explained by the well known discordance between symptom and sign in DED.[34-36]

A study by Kujawa and Rozycki[37] had found 0.05% CsA twice daily to be effective in both dry eye syndrome without systemic disease and those secondary to Sjogren's syndrome; yet in the latter group, the treatment length had been extended from 3 months to 6 months. However, for 0.1% CsA CE, through our Model 2, we did not observe an efficacy difference between autoimmune and nonautoimmune groups in a treatment length of 2 months. This inconsistency might be partially explained by the difference in disease severity and treatment length. Further studies directly evaluate the possible effectiveness difference between autoimmune and nonautoimmune are needed.

In the covariate analysis, aging was positively correlated with CFS but negatively correlated with OSDI score, which was consistent with the study from Rico-del-Viejo *et al*.[38] They reported a positive correlation in ocular surface staining with age and a negative correlation with TBUT and Schirmer's test.

Both of the key published studies 13.14 of 0.1% CsA CE had reported treatment-related adverse events in treatment naïve patients. We reported a treatment related adverse event rate of 40.1%, and 14.8% of patients discontinued due to intolerance, which was similar to Jennifer Hind1 *et al*., who reported a discontinued rate of 12%.[39] Majority of adverse events were transient instillation pain (eight patients, 29.6%), the proportion were similar to 29.2% previously reported by SANSIKA.[14] Notably, both SANSIKA and SICCANOVE [13,14] revealed that initial ocular irritation decreased with long term 0.1% CsA CE use.

Several limitations in this study should be noted. First, the present study did not include a control group. Second, there was no washout period before a change in medication was given. However, this study was not intended to be a clinical trial of CsA CE, but rather it was intended to evaluate the efficacy and safety of shifting from 0.05% CsA AE to 0.1% CsA CE in moderate-to-severe DED in a real-world setting. Third, the sample size was relatively small and with gender predilection. Finally, our result could only be applied to moderate-to-severe dry eye patients who were treated previously with 0.05% CsA AE. The benefit of 0.1% CsA CE on CsA naïve patients or mild DED patients remains unclear.

Our study provides supportive data of shifting to 0.1% CsA CE in moderate-to-severe dry eye refractory to 0.05% CsA AE. The long-term efficacy and tolerability are warranted in future studies. A prospective design trial with a larger sample size could provide a greater understanding of the comparison between the two different formulations and might be useful to aid clinical decisions in severe DED.

Ethical Statement

The study was approved and a waiver of written informed consent was granted by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan (No.: 202000799B0). All methods were performed in accordance with the declaration of Helsinki.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Chi-Chin Sun, an editorial board member at *Taiwan Journal of Ophthalmology*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

References

1. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, *et al*. TFOS DEWS II epidemiology report. Ocul Surf 2017;15:334-65.

2. Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. Am J Ophthalmol 2017;182:90-8.
3. Baudouin C. A new approach for better comprehension of diseases of the ocular surface. J Fr Ophtalmol 2007;30:239-46.
4. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, *et al.* TFOS DEWS II definition and classification report. Ocul Surf 2017;15:276-83.
5. Javadi MA, Feizi S. Dry eye syndrome. J Ophthalmic Vis Res 2011;6:192-8.
6. Perry HD, Donnenfeld ED, Kanellopoulos AJ, Grossman GA. Topical cyclosporin A in the management of postkeratoplasty glaucoma. Cornea 1997;16:284-8.
7. Barber LD, Pflugfelder SC, Tauber J, Foulks GN. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. Ophthalmology 2005;112:1790-4.
8. United Kingdom: Santen S.A.S, Ikervis, Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/6937/smpc#gref. [Last accessed on 2022 Mar 15].
9. Lallemand F, Schmitt M, Bourges JL, Gurny R, Benita S, Garrigue JS. Cyclosporine a delivery to the eye: A comprehensive review of academic and industrial efforts. Eur J Pharm Biopharm 2017;117:14-28.
10. Boboridis KG, Konstas AG. Evaluating the novel application of cyclosporine 0.1% in ocular surface disease. Expert Opin Pharmacother 2018;19:1027-39.
11. Daull P, Lallemand F, Philips B, Lambert G, Buggage R, Garrigue JS. Distribution of cyclosporine a in ocular tissues after topical administration of cyclosporine a cationic emulsions to pigmented rabbits. Cornea 2013;32:345-54.
12. Amrane M, Creuzot-Garcher C, Robert PY, Ismail D, Garrigue JS, Pisella PJ, *et al.* Ocular tolerability and efficacy of a cationic emulsion in patients with mild to moderate dry eye disease – A randomised comparative study. J Fr Ophtalmol 2014;37:589-98.
13. Baudouin C, Figueiredo FC, Messmer EM, Ismail D, Amrane M, Garrigue JS, *et al.* A randomized study of the efficacy and safety of 0.1% cyclosporine a cationic emulsion in treatment of moderate to severe dry eye. Eur J Ophthalmol 2017;27:520-30.
14. Leonardi A, Van Setten G, Amrane M, Ismail D, Garrigue JS, Figueiredo FC, *et al.* Efficacy and safety of 0.1% cyclosporine a cationic emulsion in the treatment of severe dry eye disease: A multicenter randomized trial. Eur J Ophthalmol 2016;26:287-96.
15. Leonardi A, Messmer EM, Labetoulle M, Amrane M, Garrigue JS, Ismail D, *et al.* Efficacy and safety of 0.1% ciclosporin a cationic emulsion in dry eye disease: A pooled analysis of two double-masked, randomised, vehicle-controlled phase III clinical studies. Br J Ophthalmol 2019;103:125-31.
16. Pisella PJ, Labetoulle M, Doan S, Cochener-Lamard B, Amrane M, Ismail D, *et al.* Topical ocular 0.1% cyclosporine a cationic emulsion in dry eye disease patients with severe keratitis: Experience through the French early-access program. Clin Ophthalmol 2018;12:289-99.
17. US Food and Drug Administration, Restasis® Approval Package. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-023_Restasis.cfm. [Last accessed on 2022 Mar 15].
18. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22:640-50.
19. Hwang SB, Park JH, Kang SS, Kang DH, Lee JH, Oh SJ, *et al.* Protective effects of cyclosporine a emulsion versus cyclosporine a cationic emulsion against desiccation stress in human corneal epithelial cells. Cornea 2020;39:508-13.
20. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin a ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: A dose-ranging, randomized trial. The cyclosporin a phase 2 study group. Ophthalmology 2000;107:967-74.
21. de Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine a therapy for dry eye syndrome. Cochrane Database Syst Rev 2019;9:CD010051.
22. Daull P, Amrane M, Ismail D, Georgiev G, Cwiklik L, Baudouin C, *et al.* Cationic emulsion-based artificial tears as a mimic of functional healthy tear film for restoration of ocular surface homeostasis in dry eye disease. J Ocul Pharmacol Ther 2020;36:355-65.
23. Labetoulle M, Leonardi A, Amrane M, Ismail D, Garrigue JS, Garhöfer G, *et al.* Persistence of efficacy of 0.1% cyclosporin a cationic emulsion in subjects with severe keratitis due to dry eye disease: A nonrandomized, open-label extension of the SANSIKA study. Clin Ther 2018;40:1894-906.
24. Sullivan B. Challenges in using signs and symptoms to evaluate new biomarkers of dry eye disease. Ocul Surf 2014;12:2-9.
25. Bikbova G, Oshitari T, Baba T, Yamamoto S. Neuronal changes in the diabetic cornea: Perspectives for neuroprotection. Biomed Res Int 2016;2016:1-8.
26. Al-Aqaba MA, Dhillon VK, Mohammed I, Said DG, Dua HS. Corneal nerves in health and disease. Prog Retin Eye Res 2019;73:100762.
27. Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, *et al.* TFOS DEWS II pain and sensation report. Ocul Surf 2017;15:404-37.
28. Villani E, Galimberti D, Viola F, Mapelli C, Ratiglia R. The cornea in Sjogren's syndrome: An *in vivo* confocal study. Invest Ophthalmol Vis Sci 2007;48:2017-22.
29. Labbé A, Liang Q, Wang Z, Zhang Y, Xu L, Baudouin C, *et al.* Corneal nerve structure and function in patients with Non-Sjogren dry eye: Clinical correlations. Invest Ophthalmol Vis Sci 2013;54:5144-50.
30. Toker E, Asfuroğlu E. Corneal and conjunctival sensitivity in patients with dry eye: The effect of topical cyclosporine therapy. Cornea 2010;29:133-40.
31. Steiner JP, Connolly MA, Valentine HL, Hamilton GS, Dawson TM, Hester L, *et al.* Neurotrophic actions of nonimmunosuppressive analogues of immunosuppressive drugs FK506, rapamycin and cyclosporin a. Nat Med 1997;3:421-8.
32. Lee JH, Kim JW, Im YS, Seong GJ, Lee HK. Cyclosporine a induces nerve growth factor expression via activation of MAPK p38 and NFAT5. Cornea 2011;30 Suppl 1:S19-24.
33. Levy O, Labbé A, Borderie V, Hamiche T, Dupas B, Laroche L, *et al.* Increased corneal sub-basal nerve density in patients with Sjögren syndrome treated with topical cyclosporine A. Clin Exp Ophthalmol 2017;45:455-63.
34. Bartlett JD, Keith MS, Sudharshan L, Snedecor SJ. Associations between signs and symptoms of dry eye disease: A systematic review. Clin Ophthalmol 2015;9:1719-30.
35. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. Cornea 2004;23:762-70.
36. Schein OD, Tielsch JM, Munõz B, Bandeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly. A population-based perspective. Ophthalmology 1997;104:1395-401.
37. Kujawa A, Rózycki R. A 0,05% cyclosporine treatment of the advanced dry eye syndrome. Klin Oczna 2005;107:280-6.
38. Rico-Del-Viejo L, Lorente-Velázquez A, Hernández-Verdejo JL, García-Mata R, Benítez-Del-Castillo JM, Madrid-Costa D. The effect of ageing on the ocular surface parameters. Cont Lens Anterior Eye 2018;41:5-12.
39. Hind J, Macdonald E, Lockington D. Real-world experience at a Scottish University teaching hospital regarding the tolerability and persistence with topical Ciclosporin 0.1% (Ikervis) treatment in patients with dry eye disease. Eye (Lond) 2019;33:685-6.

Supplementary Material

Supplementary Table S1: Generalized estimate equation models predicting cornea fluorescein stain score

Model/variables	*B*	95% CI	*P*
Model 1: Visit and covariates			
Age	0.090	0.007–0.174	0.033*
CsA AE duration	0.020	−0.009–0.049	0.173
Auto immune			
Yes	−0.006	−1.684–1.671	0.994
No	Reference		
Steroids			
High potency	1.890	−1.570–5.351	0.284
Low potency	2.101	−0.973–5.174	0.180
No	Reference		
Visit			
2	−0.180	−0.429–0.069	0.156
1	−0.696	−1.046–0.346	<0.001*
Baseline	Reference		
Model 2: Visit×autoimmune			
Age	0.008	−0.083–0.099	0.863
CsA AE duration	0.013	−0.013–0.039	0.341
Auto immune			
Yes	0.469	−0.366–1.305	0.271
No	Reference		
Steroids			
High potency	1.079	−1.636–3.794	0.436
Low potency	0.663	−2.216–3.542	0.652
No	Reference		
Visit			
2	−0.169	−0.635–0.297	0.477
1	−0.750	−1.421–0.079	0.028*
Baseline	Reference		
Visit 2× autoimmune	−0.031	−0.603–0.541	0.916
Visit 1× autoimmune	−0.083	−0.697–0.864	0.834

*P<0.05, generalized estimate equations. CsA AE=0.05% cyclosporine A anionic emulsion, CI=Confidence interval

Supplementary Table S2: Generalized estimate equation models predicting tear break-up time

Model/variables	*B*	95% CI	*P*
Model 1: Visit and covariates			
Age	0.019	−0.044-0.082	0.554
CsA AE duration	−0.038	−0.068-0.007	0.017*
Auto immune			
Yes	−0.652	−2.231-0.928	0.419
No	Reference		
Steroids			
High potency	4.054	−0.240-8.348	0.064
Low potency	5.194	1.104-9.285	0.013*
No	Reference		
Visit			
2	0.783	0.317-1.249	0.001*
1	0.696	0.164-1.227	0.01*
Baseline	Reference		
Model 2: Visit×autoimmune			
Age	0.021	−0.129-0.172	0.779
CsA AE duration	−0.026	−0.072-0.020	0.273
Auto immune			
Yes	−0.670	−2.010-0.670	0.327
No	Reference		
Steroids			
High potency	0.117	−4.172-4.405	0.958
Low potency	1.112	−3.376-5.601	0.627
No	Reference		
Visit			
2	1.250	0.495-2.005	0.001*
1	1.125	0.246-2.004	0.012*
Baseline	Reference		
Visit 2× autoimmune	−0.717	−1.651-0.218	0.133
Visit 1× autoimmune	−0.658	−1.744-0.427	0.235

*P<0.05, generalized estimate equations. CsA AE=0.05% cyclosporine A anionic emulsion, CI=Confidence interval

Supplementary Table S3: Generalized estimate equation models predicting cornea sensitivity

Model/variables	*B*	95% CI	*P*
Model 1: Visit and covariates			
Age	0.050	−0.034-0.133	0.242
CsA AE duration	0.008	−0.019-0.035	0.565
Auto immune			
Yes	−0.088	−1.170-0.995	0.874
No	Reference		
Steroids			
High potency	−0.949	−3.802-1.904	0.514
Low potency	−0.023	−2.074-2.029	0.983
No	Reference		
Visit			
2	0.258	0.011-0.505	0.041*
1	0.630	0.167-1.094	0.008*
Baseline	Reference		
Model 2: Visit×autoimmune			
Age	0.042	−0.036-0.120	0.293
CsA AE duration	0.008	−0.016-0.033	0.513
Auto immune			
Yes	0.395	−1.015-1.805	0.583
No	Reference		
Steroids			
High potency	−0.843	−3.377-1.691	0.514
Low potency	−0.123	−2.027-1.782	0.899
No	Reference		
Visit			
2	0.339	−0.144-0.822	0.169
1	0.938	−0.94-1.969	0.075
Baseline	Reference		
Visit 2×autoimmune	−0.105	−0.665-0.454	0.712
Visit 1×autoimmune	−0.471	−1.587-0.646	0.409

*P<0.05, generalized estimate equations. CsA AE=0.05% cyclosporine A anionic emulsion, CI=Confidence interval

Supplementary Table S4: Generalized estimate equation models predicting ocular surface disease index

Model/variables	*B*	95% CI	*P*
Model 1: Visit and covariates			
Age	−1.530	−2.386-−0.673	0.000*
CsA AE duration	0.429	0.060-0.798	0.023*
Auto immune			
Yes	−9.863	−25.699-5.974	0.222
No	Reference		
Steroids			
High potency	45.150	21.859-68.441	0.000*
Low potency	11.631	−3.058-26.319	0.121
No	Reference		
Visit			
2	−2.035	−6.968-2.898	0.419
1	1.135	−3.813-6.083	0.653
Baseline	Reference		
Model 2: Visit×autoimmune			
Age	−1.423	−2.073-−0.774	0.000*
CsA AE duration	0.298	−0.030-0.625	0.075
Autoimmune			
Yes	−7.763	−24.831-9.305	0.373
No	Reference		
Steroids			
High potency	26.885	4.821-48.949	0.017*
Low potency	11.984	−5.597-29.566	0.182
No	Reference		
Visit			
2	−3.120	−14.237-7.998	0.582
1	1.275	−5.625-8.175	0.717
Baseline	Reference		
Visit 2× autoimmune	1.546	−10.515-13.608	0.802
Visit 1× autoimmune	−0.215	−9.787-9.357	0.965

*P<0.05, Generalized estimate equations. OSDI=Ocular surface disease index questionnaire, CsA AE=0.05% cyclosporine A anionic emulsion, CI=Confidence interval

Supplementary Table S5: Generalized estimate equation models predicting Schirmer's test score

Model/variables	*B*	95% CI	*P*
Model 1: Visit and covariates			
Age	0.011	−0.504-0.527	0.965
CsA AE duration	0.104	−0.098-0.305	0.313
Autoimmune			
Yes	−5.181	−14.367-4.006	0.269
No	Reference		
Steroids			
High potency	19.475	3.449-35.500	0.017*
Low potency	9.975	−4.008-23.958	0.162
No	Reference		
Visit			
2	1.528	−1.070-4.127	0.249
1	0.913	−1.015-2.841	0.353
Baseline	Reference		
Model 2: Visit×autoimmune			
Age	0.021	−0.491-0.534	0.935
CsA AE duration	0.095	−0.102-0.293	0.345
Auto immune			
Yes	−6.131	12.472-0.210	0.058
No	Reference		
Steroids			
High potency	18.711	3.303-34.118	0.017*
Low potency	9.523	−3.558-22.605	0.154
No	Reference		
Visit			
2	1.446	−4.122-7.013	0.611
1	1.125	−3.068-5.318	0.599
Baseline	Reference		
Visit 2× autoimmune	0.088	−6.012-6.188	0.978
Visit 1× autoimmune	−0.325	−4.941-4.201	0.890

*P<0.05, Generalized estimate equations. CsA AE=0.05% cyclosporine A anionic emulsion, CI=Confidence interval