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Outcomes of Topical Cyclosporine 0.1% in Patients with Moderate-to-Severe Dry Eye Disease Unresponsive to Cyclosporine 0.05%

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Background: Dry eye disease (DED) is a complex, chronic inflammation of the ocular surface that can severely impact vision and quality of life. While 0.05% topical cyclosporine is a cornerstone of therapy, a significant subset of patients with moderate-to-severe DED continue to experience persistent symptoms and signs despite long-term treatment.

Aim: To investigate the efficacy and safety of switching to 0.1% topical cyclosporine in patients with moderate-to-severe DED who remained refractory to standard 0.05% therapy.

Methods: In a 12-week, open-label, prospective study, adult patients unresponsive after ≥12 weeks of 0.05% cyclosporine were transitioned to 0.1% cyclosporine and monitored closely. The primary endpoint was change in symptom severity (via the Ocular Surface Disease Index [OSDI] and Symptom Assessment in Dry Eye [SANDE] questionnaires). Secondary outcomes included tear-film break-up time (TBUT), Schirmer I test values, corneal and conjunctival staining, and tear volume. Safety was assessed through the incidence of treatment-emergent adverse events (TEAEs).

Results: Ninety-one patients were enrolled, with seventy completing the study. At 12 weeks, patients showed robust and statistically significant improvements in symptom scores (SANDE, $p < 0.0001$), corneal and conjunctival staining ($p < 0.0001$), TBUT ($p < 0.0001$), and tear volume ($p < 0.0001$) compared with baseline. The mean reduction in subjective dryness was –7.48 (95% CI: –14.5 to –0.82). The 0.1% formulation was well tolerated; the most common TEAEs were transient burning and ocular hyperemia. There were no significant IOP elevations or serious ocular adverse events reported.

Conclusion: For patients with moderate-to-severe DED unresponsive to 0.05% topical cyclosporine, switching to 0.1% offers a compelling therapeutic benefit—yielding meaningful improvements in both subjective symptoms and objective ocular-surface parameters. The enhanced concentration and optimized formulation appear able to overcome prior treatment limitations. These findings support the need for larger randomized controlled trials to validate and refine individualized treatment strategies in severe DED.

I. INTRODUCTION-

Dry eye disease (DED) represents one of the most prevalent ocular surface disorders worldwide, though its reported incidence varies owing to differences in definitions and diagnostic criteria. Women and the elderly population consistently exhibit a higher susceptibility. With the global rise in digital screen exposure and the steady aging of populations, the burden of visual discomfort and disturbance associated with DED is anticipated to escalate further.Thepathogenesis of DED is multifactorial, characterized by a complex interplay among tear film instability, ocular surface inflammation, epithelial damage, and neurosensory dysfunction. The disease often perpetuates a vicious inflammatory cycle, necessitating targeted therapeutic interventions beyond conventional tear substitutes.Among the available anti-inflammatory therapies, Cyclosporine A (CsA) has emerged as a cornerstone agent. Unlike corticosteroids, CsA does not induce cataractogenesis or elevate intraocular pressure, thereby offering a safer profile for long-term management of chronic ocular surface inflammation.To enhance its ocular bioavailability, a cationic oil-in-water emulsion of 0.1% CsA (CsA CE) was developed. This novel formulation prolongs corneal contact time through electrostatic interaction between the positively charged emulsion droplets and the negatively charged mucins within the tear film.Clinical evidence from two pivotal phase-III randomized controlled trials and their pooled analysis has demonstrated that CsA CE significantly alleviates both the signs and symptoms of DED, improving corneal fluorescein staining scores and patient-reported discomfort. With an excellent safety and tolerability profile, CsA CE stands as a major advancement in the long-term pharmacologic management of moderate to severe dry eye disease.

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II. MATERIALS AND METHODS

Case selection and study design

This retrospective case-series evaluated consecutive patients diagnosed with moderate-to-severe dry eye disease (DED) and managed at a single institution. A total of 23 adult patients (≥18 years), including 10 with Sjögren's syndrome and 5 with Rheumatoid arthritis, were reviewed. Institutional chart review was approved, and a waiver of written informed consent was granted by the relevant ethics committee.Inclusion criteria were: a corneal fluorescein staining (CFS) score of 3, 4, or 5 on the modified Oxford scale (indicating moderate to severe DED); prior inadequate response to twice-daily topical 0.05% cyclosporine A anionic emulsion (CsA AE) for at least 3 months in conjunction with artificial tears; age ≥18 years. Concomitant steroid use, when present, was either 0.1% fluorometholone TID or 0.1% betamethasone TID. Patients were excluded if they had a history of ocular trauma, infection, or non-DED inflammation within the previous 3 months; required topical ocular treatment for other ocular conditions during the study period; wore contact lenses; or required adjustment of topical medications other than CsA during the study. Patients who discontinued 0.1% CsA cationic emulsion (CsA CE) before the first follow-up visit were excluded from efficacy analysis.

Treatment Protocol and Visits

All eligible patients were transitioned from twice-daily 0.05% CsA AE to once-daily 0.1% CsA CE for a two-month period. The timepoint of switching to 0.1% CsA CE was defined as baseline (Visit 0). Follow-up Visit 1 occurred after two months of 0.1% CsA CE therapy. Subsequently, patients were shifted back to twice-daily 0.05% CsA AE, and the first clinic visit after this switch was defined as Visit 2. Dry-eye parameters were recorded and compared at each visit, with efficacy analysis performed on the worst eligible eye (defined as the eye with the higher baseline CFS score). Treatment-related adverse events were documented throughout.

III. DATA COLLECTION

Demographic data, systemic disease profile, ocular examination records, concomitant medications, and treatment-related adverse effects were extracted from patient charts. The following dry eye parameters were assessed at each visit

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 biomicroscopyimage 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

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. Or we can use a wisp of cotton to check corneal sensitivity

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.

IV. STATISTICAL ANALYSIS

All continuous variables, including Schirmer's test score, tear break-up time (TBUT), corneal sensitivity, corneal fluorescein staining (CFS) score, and Ocular Surface Disease Index (OSDI) score, were summarized as mean ± standard deviation (SD). The normality of data distribution was verified using the Shapiro–Wilktest.Baseline demographic and clinical characteristics were compared using the independent-samples t-test for quantitative variables and the Chi-square test for categorical variables. Changes in best-corrected visual acuity (BCVA) and intraocular pressure (IOP) before and after switching to 0.1% cyclosporine cationic emulsion (CsA CE) were analyzed using the paired t-test.

To evaluate longitudinal changes in dry-eye parameters across visits (baseline, Visit 1, and Visit 2), a generalized estimating equation (GEE) model was employed to account for intra-subject correlation between repeated measures. Treatment period (medication type: 0.05% CsA AE vs. 0.1% CsA CE) served as the main independent variable. Covariates included age, duration of prior 0.05% CsA AE use, presence of autoimmune disease, and concurrent topical steroid use (categorized as low-potency fluorometholone, high-potency betamethasone, or none). An interaction term between treatment period and autoimmune status was incorporated to determine whether treatment efficacy differed between autoimmune and non-autoimmune subgroups.All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Data were analyzed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

V. RESULTS

Patient demographics

From an initial pool of 27 patients (25 females, 2 males) who met the inclusion and exclusion criteria, four were excluded from the efficacy analysis because they discontinued the 0.1% CsA CE regimen prior to Visit 1 (three due to instillation pain, one due to sticky sensation). The remaining 23 patients (22 females, 1 male) were included in the full review. Their mean age was 61.6 ± 10.1 years. At baseline, the mean corneal fluorescein staining (CFS) score was 3.96 ± 0.82, consistent with moderate-to-severe dry eye disease. The cohort had been on 0.05% CsA AE for a mean duration of 35.8 ± 24.1 months before switching to 0.1% CsA CE. Adjunctive therapy prior to baseline included 0.1% fluorometholone three times daily in 15 patients (65.2%) and 0.1% betamethasone three times daily in 5 patients (21.7%); the remaining 3 patients (13.0%) received no topical steroids. No changes in steroid type or dosage occurred during the study period.Patients with autoimmune disease (defined as a diagnosis of Sjögren’s syndrome or rheumatoid arthritis) comprised 10 (43.5%) and 5 (21.7%) of the cohort, respectively. In the autoimmune subgroup, the mean age was 61.1 ± 10.0 years and the mean baseline CFS score was 4.2 ± 0.77; in the non-autoimmune subgroup the mean age was 62.6 ± 11.0 years and mean CFS was 3.5 ± 0.76. The difference in baseline CFS between the two subgroups approached, but did not reach, statistical significance (P = 0.05). Baseline demographic and clinical characteristics for all patients and for the autoimmune vs non-autoimmune subgroups are shown in Table 1 and Table 2 respectively

Efficacy analysis

In order to assess the therapeutic response to 0.1% CsA CE (following an inadequate response to 0.05% CsA AE), we employed a generalized estimating equation (GEE) approach with adjustment for key covariates (age; prior duration of 0.05% CsA AE therapy; presence of underlying autoimmune disease; and baseline concurrent topical steroid use).For corneal fluorescein staining (CFS), the adjusted mean ± SD values were 3.51 ± 0.56 at baseline, 2.81 ± 0.70 at Visit 1, and 3.33 ± 0.61 at Visit 2 — reflecting a significant improvement after switching to 0.1% CsA CE, followed by partial worsening after returning to 0.05% CsAAE.Corneal sensitivity improved from 4.76 ± 0.45 mm at baseline to 5.39 ± 0.36 mm at Visit 1, then declined to 5.02 ± 0.40 mm at Visit 2 — mirroring the CFS changes and indicating enhanced ocular surface nerve function post-switch.Tear film break-up time (TBUT) increased from 0.91 ± 0.72 s at baseline to 1.61 ± 0.75 s at Visit 1, with a further rise to 1.70 ± 0.83 s at Visit 2 — demonstrating a sustained and progressive improvement in tear film stability even after reversion to 0.05% CsAAE.There were no statistically significant changes in Ocular Surface Disease Index (OSDI) scores or Schirmer’s test values throughout the study period

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

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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 presents Model 1's generalized estimating equation (GEE) analysis for each dry-eye parameter (covariate effects omitted; see Supplementary Tables S1-S5 for full details). In Model 1 — which adjusts for age, prior duration of 0.05% CsA AE use, underlying autoimmune disease and baseline topical steroid use — the following was observed when comparing Visit 1 to baseline:

For corneal fluorescein-staining (CFS): B = −0.696, 95% CI [−1.046, −0.346], P < 0.001 — indicating a statistically significant improvement.

For tear-film break-up time (TBUT): B = 0.696, 95% CI [0.164, 1.227], P = 0.01 — likewise significant.

For corneal sensitivity: B = 0.630, 95% CI [0.167, 1.094], P = 0.008 — also significant.

No significant changes were detected for OSDI score (P = 0.653) or Schirmer's test (P = 0.353).

Notably, in Model 1 the effect of switching from 0.1% CsA CE back to 0.05% CsA AE (i.e., Visit 2 compared with Visit 1) revealed continuing improvement in TBUT: B = 0.783, 95% CI [0.317, 1.249], P = 0.001.

To further explore the post-treatment phase (Visit 2 vs. Visit 1) in this basic model, the following changes were observed: CFS deteriorated (B = −0.516, 95% CI [−0.839, −0.139], P = 0.002) and corneal sensitivity also worsened (B = 0.373, 95% CI [0.031, 0.714], P = 0.033). No significant change occurred in OSDI or Schirmer's scores during this interval.

Next, in Model 2 we assessed whether the treatment effect differed between the autoimmune and non-autoimmune subgroups by including an interaction term (medication × autoimmune-status). The interaction term was not significant for any parameter (see Table 4), indicating that the efficacy of 0.1% CsA CE was comparable in patients with and without autoimmune disease.

In the covariate analyses:

Older age correlated with worse baseline CFS (B = 0.09, 95% CI [0.007, 0.174], P = 0.033) and paradoxically with lower OSDI score (B = −1.53, 95% CI [−2.386, −0.673], P <0.001).Longer prior duration of 0.05% CsA AE therapy was negatively associated with TBUT (B = −0.038, 95% CI [−0.068, −0.007], P = 0.017) and positively associated with OSDI score (B = 0.429, 95% CI [0.060, 0.798], P = 0.023).

Safety analysis

Newly developed treatments related adverse eventswere reported in eleven of 27 patients (40.1%), whilebfour (14.8%) discontinued due to intolerance. The mostcommonly reportedadverse effect was instillation pain,which was reported in eight patients (29.6%). The majority

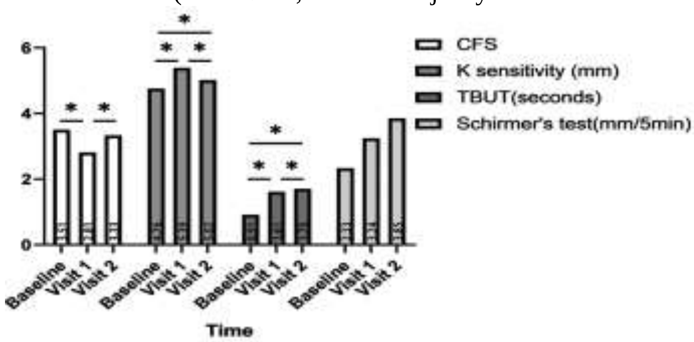

Fig 1. Graph represents change in each dry eye parameters from baseline to visit1 and visit 2 . p <0.05 .CFS , cornea fl stain , TBUT

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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 fluoresceinstain, OSDI=Ocular surface disease index, TBUT=Tear break‑ up time

Table 3: Results from generalized estimate equationpredicting 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=Tearbreak‑ up time, CFS=Cornea fluorescein stain, OSDI=Ocular surface diseaseindex

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 surfacedisease index, TBUT=Tear break‑ up time, CFS=Cornea fluorescein stain,CI=Confidence interval of instillation pain was mild and transient (<15 min). Twopatients (7.4%) reported tearing, two patients (7.4%)reported eye irritation, one patient (3.7%) reported eyeredness and one patient (3.7%) reported pruritus. Therewas no treatment‑ related serious adverse events notedthroughout the study. Moreover, during the study, therewas no significant change in visual acuity and intraocularpressure .

VI. DISCUSSION

This retrospective case-series demonstrates that switching patients with moderate-to-severe dry eye disease — refractory to long-term use of 0.05% CsA anionic emulsion (CsA AE) — to 0.1% CsA cationic emulsion (CsA CE) resulted in marked improvements in objective ocular surface signs.In clinical practice, many patients persistently suffer keratitis or other signs of ocular-surface damage despite extended use of 0.05% CsA AE. The enhanced formulation and higher concentration of CsA CE have been shown in randomized trials to improve corneal fluorescein staining (CFS) and inflammatory markers compared with vehicle. Preclinical workalso supports superior anti-inflammatory and anti-apoptotic actions of the cationic emulsion versus the anionic form. In our cohort, tear-film break-up time (TBUT) improved significantly after 0.1% CsA CE and appeared to maintain or even continue improving after revert-switching to 0.05% CsA AE, suggesting a possible sustained tear-film stabilising effect. CFS and corneal sensitivity also improved after the switch, but worsened again once the 0.1% CsA CE was discontinued. We believe the limited duration of CsA CE exposure (2 months) may account for this partial regression, compared with longer extension studies (e.g., the SANSIKA Study) where worsening after discontinuation was less evident. Corneal sensitivity, increasingly recognised as a biomarker of ocular-surface health and innervation, also improved with the switch — suggesting possible neural regeneration or improved nerve function in the more favourable micro-environment created by the cationic CsA formulation. By contrast, subjective symptom scores (OSDI) and aqueous-tear production (Schirmer's test) did not change significantly. The lack of symptom-sign correlation in dry-eye disease is well known, and our findings align with that discordance.Interestingly, in subgroup analysis we did not detect a difference in treatment efficacy between autoimmune (e.g., Sjögren's or rheumatoid arthritis) and non-autoimmune patients. While speculative in our small cohort and short duration, this may suggest the immunomodulatory effects of CsA CE are broadly applicable regardless of underlying systemic disease.In the covariate analysis: older age was associated with worse CFS but surprisingly with lower (better) OSDI score. Longer prior duration of 0.05% CsA AE use was associated with worse TBUT and higher OSDI, perhaps reflecting a more recalcitrant disease course in those patients. These findings resonate with previous reports of age-related worsening of ocular-surface staining and symptom-sign dissociation.Limitations must be acknowledged. Our study lacked a parallel control group and a wash-out period, so the design cannot establish causal inference the same way a randomised trial would. The sample size was modest and female-predominant; the 2-month duration of 0.1% CsA CE may have been insufficient for maximal clinical effect. Also, our findings apply to moderate-to-severe DED patients already treated with 0.05% CsA AE — extrapolation to treatment-naïve or mild-DED patients is not supported by our data.

VII. CONCLUSION

In summary, our real-world data provide encouraging support for the strategy of switching to 0.1% CsA CE in moderate-to-severe dry-eye disease unresponsive to 0.05% CsA AE. The improvements in objective signs of ocular-surface health merit further study in larger, prospective trials with longer follow-up, to clarify long-term efficacy, tolerability and cost-effectiveness of the higher-dose cationic formulation when compared head-to-head with the standard anionic emulsion

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

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Conflicts of interest There are no conflicts of interest in writing thispaper.

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