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Clinical efficacy of 0.1% cyclosporine A in dry eye patients with inadequate responses to 0.05% cyclosporine A: a switching, prospective, open-label, multicenter study

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Abstract

Purpose To assess the clinical efficacy of 0.1% cyclosporine A (CsA) in dry eye patients who have shown inadequate responses to previous treatment with 0.05% CsA.

Design This study was designed as a switching, prospective, multicenter, 12-week, open-label study.

Methods Patients with dry eye disease (DED), who experienced inadequate responses to at least 3 months of treatment with 0.05% cyclosporine, were enrolled in this study. Clinical evaluations included the National Eye Institute (NEI) corneal and conjunctival staining scores, tear film break-up time (TF-BUT), Symptom Assessment in Dry Eye (SANDE), ocular discomfort scale (ODS), and tear volume. These parameters were assessed at baseline, and again at 4, 8, and 12 weeks after switching to 0.1% CsA.

Results Ninety-one patients were enrolled in the study, and 70 patients completed the trial. Statistical analysis was performed on the full analysis set (FAS) using the Markov Chain Monte Carlo (MCMC) method to account for missing data. After switching to 0.1% CsA, subjective symptoms assessed by the Symptom Assessment in Dry Eye (SANDE) and Ocular Discomfort Scale (ODS) showed improvement ($p < 0.0001$). Objective signs of dry eye, including the National Eye Institute (NEI) score, tear film break-up time (TF-BUT), and tear volume also improved ($p < 0.0001$).

Conclusions In patients with dry eye disease (DED) who exhibited inadequate responses to 0.05% cyclosporine A (CsA), switching to 0.1% CsA resulted in significant improvements in both subjective symptoms and objective clinical signs. This finding suggests that higher concentrations of CsA may be more effective in treating individuals with moderate to severe DED.

Keywords Dry eye disease, Cyclosporine A, Cationic emulsion, Switching, Multicenter study

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Introduction

Dry eye disease (DED) is defined as a multifactorial disease of the ocular surface characterized by a loss of the tear film homeostasis with various ocular symptoms [1]. Tear instability leads to tear hyperosmolarity, which damages the ocular surface and triggers inflammatory responses [2]. Since this inflammation ultimately results in chronic ocular surface damage and induce clinical symptoms and signs, controlling ocular surface inflammation is essential for relieving the symptoms and signs of DED [3–5]. Therefore, anti-inflammatory therapy, including the use of topical corticosteroids and cyclosporine A, is considered a key factor in the successful treatment of DED [6, 7].

CsA was isolated from the fungus *Tolypocladium inflatum* and is well known for blocking the T cell infiltration, and activation and the subsequent release of inflammatory cytokines [8]. Although topical steroid provides several benefits to control the ocular surface inflammation including DED, it might provoke some complications such as cataract progression and high intraocular pressure in long term use [9]. There have been many clinical trials to prove the efficacy of topical CsA in moderate to severe DED and to avoid the complications caused by steroid use [10–12]. Although both concentrations of 0.05% and 0.1% CsA showed significant effects compared to the vehicle, a clear dose-response effect was not observed among the different drug concentrations, and 0.05% CsA anionic emulsion (Restasis®, Allergan, Irvine, CA, US) was approved by US Food and Drug Administration (FDA) as a first CsA ophthalmic solution [13]. Although there are many cases of successful treatment of DED with 0.05% CsA, there are also numerous instances of inadequate response. To enhance treatment efficacy, various formulations and concentrations of CsA medications are being developed and used [14, 15].

0.1% CsA (Ikervis®Santen, Evry, France) is a cationic emulsion (CE) which has reported a good drug delivery in experiments [16]. In clinical trials, 0.1% CsA CE reduced the corneal fluorescein staining and inflammatory marker level in moderate to severe DED [17, 18]. In patients with Sjögren's syndrome, 0.1% CsA CE have been showed effective outcomes after switching to 0.1% CsA [19]. However, there have been no studies conducted in non-Sjögren's patients with moderate to severe DED. For these reasons, a prospective multicenter clinical trial was needed to identify the effectiveness of 0.1% CsA in patients with DED with inadequate effects from previous treatment with 0.05% CsA. In this study, we focused on the clinical efficacy of switching to 0.1% CsA from 0.05% CsA in Sjögren's and non Sjögren's patients with dry eye with inadequate effects from previous treatment.

Methods

Study design

This prospective, multicenter, 12-week, open-label study conducted at eight medical centers in Korea. Patients who were inadequate response to 0.05% topical CsA applied twice daily for at least 3 months were included in this study. The inadequate response was considered if (1) the Symptom Assessment in Dry Eye (SANDE) score was ≥ 40, (2) corneal staining score (National Eye Institute grading system) was ≥ 3, (3) Tear Film Break-up Time (TF-BUT) was ≤ 10 s, (4) tear volume by tear meniscometry was < 5 mm, and (5) involved one or more symptoms including burning, stinging, itching sensation, and blurry vision.

Study papulation

A screening visit was conducted for participants aged between 19 and 80 years who had used 0.05% topical CsA for 3 months but experienced inadequate response. Patients were asked whether they had used any eye drops other than 0.05% CsA. All the patients stopped all the other eyedrops except artificial tears and 3% diquafosol until the end of study. They were then given a 2-week washout period during which they continued to use preservative-free artificial tears or 3% diquafosol tetrasodium eye drops containing 0.05% CsA, while all other ophthalmic medications were discontinued. If there were no prohibited drugs, the patients started baseline visit immediately without 2 weeks washout. The following visits consisted of 3 visits over 12 weeks (4, 8, and 12 weeks) using 0.1% topical CsA CE with one drop once a day at bedtime with continuous use of unpreserved artificial tears or 3% diquafosol tetrasodium eyedrops which were identified during the screening visit (Fig. 1).

At baseline visit, they were switched to 0.1% topical CsA CE applied once daily from 0.05% topical CsA. The exclusion criteria were as follows: (1) use of topical

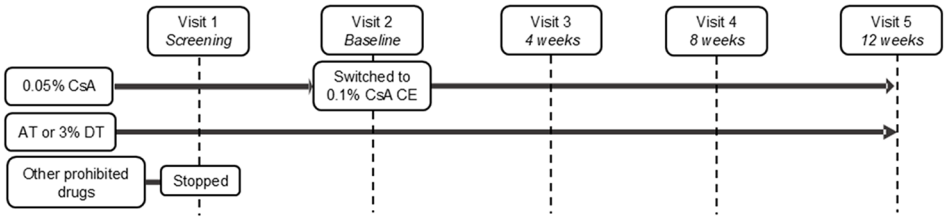

Fig. 1 Study design. CsA = cyclosporine A, AT = Artificial tears, DT = Diquafosol tetrasodium, CE = Cationic emulsion

eyedrops such as steroid, anti-glaucoma, anti-allergy, and anti-inflammation drugs or systemic steroids within 4 weeks, (2) recent use of immunomodulators for uncontrolled systemic disease for or the dose changed within 4 weeks, (3) presence of severe pterygium or Meibomian gland dysfunction, (4) a history of ocular or laser surgery within 3 months before study enrollment, (5) contact lens user, (6) past or active ocular infection and inflammation.

Efficacy assessments

At each visit, SANDE and ocular discomfort scale (ODS) questionnaire, NEI ocular staining score in cornea and conjunctiva, TF-BUT, and tear volume were evaluated. For the analysis of NEI ocular staining score, ODS questionnaire, NEI ocular staining score, TF-BUT, and tear volume, the eye with worse NEI ocular staining score of cornea was chosen. When both the eyes had the same value, the right eye was chosen for analysis.

All clinical assessments were done in the order of assessing TF-BUT, corneal and conjunctival staining, SANDE score, tear volume assessment, and ODS evaluation. TF-BUT was assessed through recording the time interval between the last complete blinking and the first appearance of a dry spot or disruption of the tear film with a moistened fluorescein strip (Haag-Sterit, Koeniz, Switzerland). Corneal and conjunctival staining scores were determined the total scores which sum of the separated 5 and 6 regions by NEI workshop after fluorescein staining. Each region was recorded quantitatively as 0–3 (0 = no staining, 1 = few punctate spots that can easily be counted, 2 = moderate staining, or more punctate spots than can easily be counted, 3 = dense punctate staining that have coalesced). Conjunctival staining scores were assessed under the yellow filter.

SANDE is a short and intuitive questionnaire based on a visual analog scale that quantifies both severity and frequency of dry eye symptoms. SANDE comprises two questions and each question employs a 100 mm horizontal linear visual analog scale and the mean of two scores is used. The measurement of symptom frequency ranges from "rarely" to "all of the time," and the symptom severity from "very mild" to "very severe." ODS consists of four questions about the following symptoms of dry eye syndrome: burning or stinging, foreign body sensation, itching sensation, and blurred vision. Symptom severity is assessed on a scale from 0 to 40, with scores of 0–10 for each category.

Tear volume was estimated using strip meniscometry (SMTube. Echo Electricity Co., Ltd., Fukushima, Japan) which had a good correlation with Schirmer's test [20]. The examiner immersed the tip of the strip into the tear meniscus of the lower eyelid for 5 s to absorb tears, causing the attached SMTube to turn blue as it indicates the volume, after which the strip was removed and the length of the blue-stained column was measured.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences v23.0 software for Windows (SPSS, Inc., Chicago, IL). The results are expressed as means ± standard deviations in numerical data and frequency (fraction) in categorical data. Statistical analysis was done on the full analysis set (FAS) and per protocol set (PP). FAS comprised all patients and multiple imputation with Markov Chain Monte Carlo (MCMC) method was applied for missing data. Missing data were considered as the patients who dropped out with any protocol deviation and showed the medication compliance under 70% based on the following calculation. PP comprised patients who completed the scheduled study except missing data which described as above. Medication compliance was defined as percentage that the days used study medication once a day per follow up days.

The primary efficacy endpoint of this study was the difference of corneal staining score between baseline and 12 weeks with pared t-test or singed rank test. The secondary efficacy endpoint included as follows: (1) The differences of corneal staining score at each visit prepared to baseline and over 12 weeks, (2) The differences of conjunctival staining score, TF-BUT, tear volume, SANDE, and ODS between baseline and 12 weeks, at each visit prepared to baseline and over 12 weeks, (3) The improvement rate of SANDE (including more than 10% of score change) between each visit with baseline, (4) Patient reported outcome (PRO) at 12 weeks. The t-test or singed rank test was used to analyze the difference between baseline and 12 weeks. Generalized estimating equation was used to analyze over 12 weeks and contrast for multiple comparison. The probability values < 0.05 were considered significant.

Sample size calculations were based on the results of a previous studies on dry eyes. The expected effect difference of CSS from baseline and standard deviation were 1 and 2.5, respectively. The expected no effect of CSS was 0. On setting the risk α at 5% and the power at 90%, around 72 evaluable patients were needed to detect a significant difference compared to baseline. Accounting for non-evaluable patients (approximately 20%), a total of 90 patients were to be recruited.

Safety assessment

The safety analysis set was used for reporting the safety data that included all patients for this trial. This included all adverse events (AE) and adverse drug reactions (ADR) regardless of any evidence which were used in study medication throughout the study (all visits from baseline to 12 weeks).

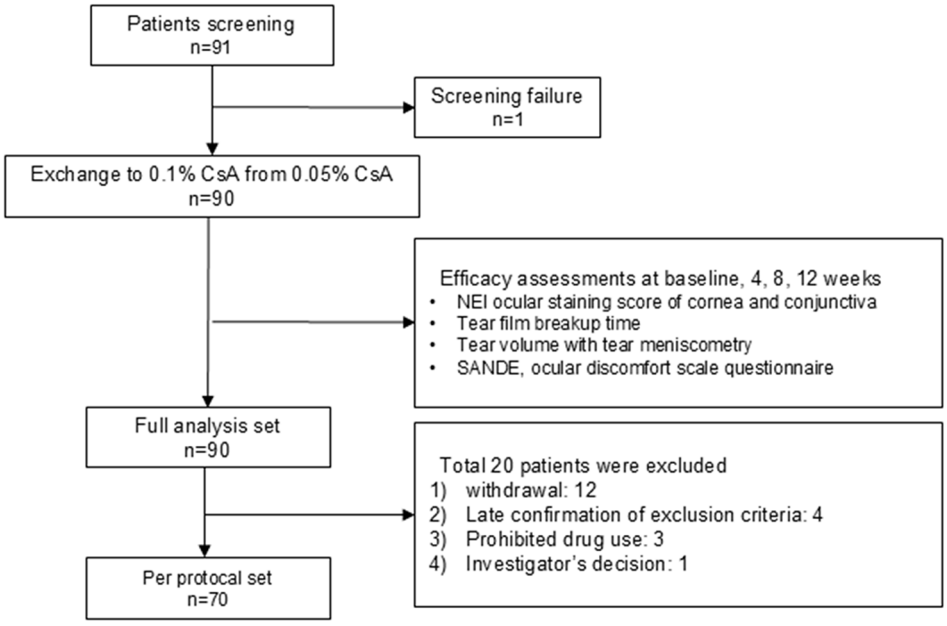

Fig. 2 Patient flow during this study. CsA = cyclosporine A, NEI = The National Eye Institute, SANDE = Symptom Assessment in Dry Eye

Table 1 Baseline demographic characteristics

Characteristics	Total ($n = 90$)
Age, years	57.99 ± 12.56
Sex, M:F	5 : 85
TBUT, seconds	4.28 ± 1.22
Ocular staining score(NEI)	
Corneal staining score	4.52 ± 2.41
Conujnctival staining score	2.09 ± 3.86
SANDE	67.69 ± 16.50
ODS	17.30 ± 7.24
Tear volume	2.81 ± 1.64

All continuous variables are presented as mean ± standard deviation

N = numbers, M = male, F = female, TBUT = Tear film breakup time, NEI = The National Eye Institute, SANDE = Symptom Assessment in Dry Eye, ODS = ocular discomfort scale

Results

This study was conducted between October 2020 and March 2022. A total of 91 patients diagnosed with DED with inadequate effects from previous topical 0.05% CsA treatment and 90 patients including 11 patients with Sjogren's syndrome underwent the study protocol (Fig. 2). A total of 56 patients (62.2%) used hyaluronic acid artificial tears, 18 patients (20%) used carboxymethyl cellulose artificial tears, 1 patient (1.1%) used 3% diquafosol, and 15 patients did not use other eyedrops. During this study, a total of 17 patients withdrew from the study early. This included 12 patients who withdrew their consent, four patients who used prohibited medications after trial registration, and one patient who was withdrawn by the investigator's decision. This included an additional three patients who determined the exclusion by the investigator after the end of this study; 70 patients were set as per protocol set (PP) and 90 patients as FAS. The baseline clinical characteristics of the patients are summarized in Table 1. Seventy-four patients (82.22%) out of a total 90 patients had other systemic disease history including Sjogren's syndrome (11 cases), rheumatoid arthritis (1 case), diabetic mellitus (14 cases), atopic dermatitis (1 case), hypothyroidism (7 cases), and others (Supplement 1).

In both FAS set and PP populations, the corneal and conjunctival staining scores showed significant changes over 12 weeks ($p < 0.0001$). The corneal staining score in FAS showed 4.52 ± 2.41 at baseline, 1.64 ± 1.51 at 4 weeks, 1.25 ± 1.39 at 8 weeks, and 1.04 ± 1.76 at 12 weeks. In PP papulations, the corneal staining score showed 4.39 ± 1.96 at baseline, 1.70 ± 1.52 at 4 weeks, 1.21 ± 1.40 at 8 weeks, and 1.01 ± 1.50 at 12 weeks. Each visit had statistically significant difference with baseline (all $p < 0.0001$). The primary end point (corneal staining score difference between baseline and 12 weeks) had significant difference in both FAS and PP ($p < 0.0001$). The conjunctival staining score showed 2.09 ± 3.86 at baseline, 1.43 ± 3.13 at 4 weeks ($p < 0.05$), 1.14 ± 2.59 at 8 weeks ($p < 0.01$), and 1.02 ± 2.63 at 12 weeks ($p < 0.001$) with statistical significance in FAS. The conjunctival staining score in PP showed 2.03 ± 3.72 at baseline, 1.37 ± 3.10 at 4 weeks ($p < 0.05$), 1.09 ± 2.63 at 8 weeks ($p < 0.01$), and 0.96 ± 2.69 at 12 weeks ($p < 0.001$) with same statistical results as FAS. Conjunctival staining score difference between baseline and 12 weeks had significant difference in both FAS and PP ($p < 0.0001$). (Fig. 3).

There were significant changes over 12 weeks in TF-BUT, mean SANDE, ODS, and tear volume (all $p < 0.0001$). TF-BUT was 4.28 ± 1.22 at baseline,

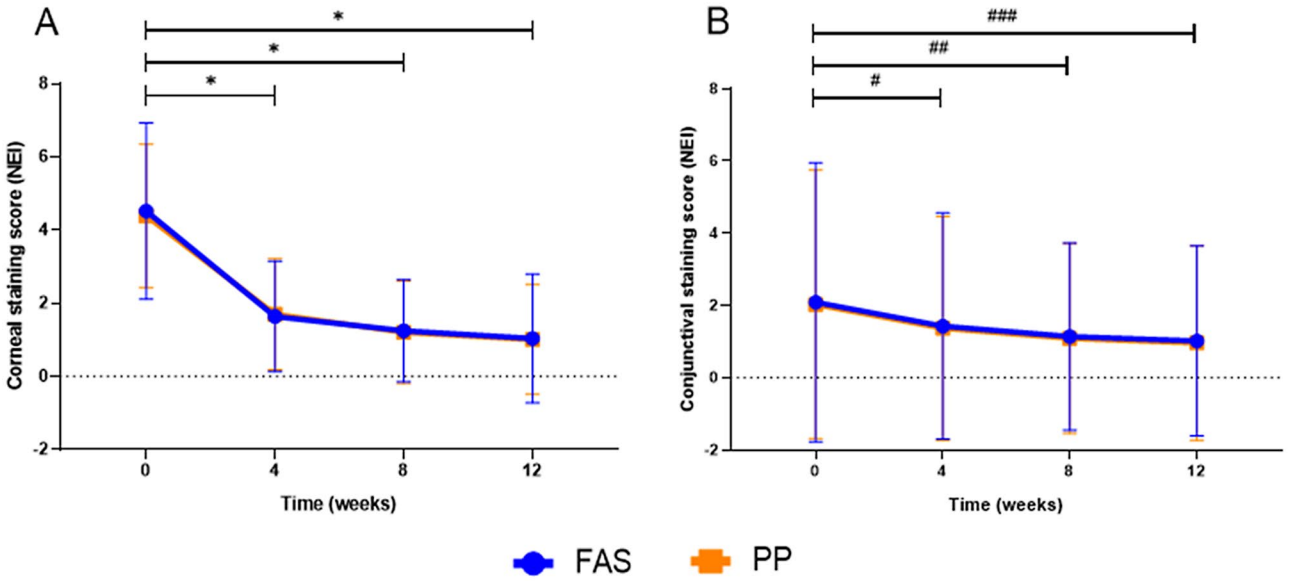

Fig. 3 Changes in the corneal and conjunctival staining score over 12 weeks after switching to 0.1% from 0.05% cyclosporine A in FAS and PP. **A**. Corneal staining score: All corneal staining score differences compared to baseline at each visit showed significant improvement (all $p < 0.0001$). The change by time showed significance (both $p < 0.0001$). **B**. Conjunctival staining score: All conjunctival staining score differences compared to baseline at each visit showed significant improvement (all $p < 0.05$). The change by time showed significance (both $p < 0.0001$). NEI = The National Eye Institute, FAS = full analysis set, PP = per protocol set. *: $p < 0.0001$. #: $p < 0.05$, ##: $p < 0.01$, ###: $p < 0.001$

5.21 ± 1.35 at 4 weeks ($p < 0.0001$), 5.35 ± 1.43 at 8 weeks ($p < 0.0001$), and 5.55 ± 1.53 at 12 weeks ($p < 0.0001$) in FAS, and 4.29 ± 1.21 at baseline, 5.20 ± 1.30 at 4 weeks ($p < 0.0001$), 5.37 ± 1.43 at 8 weeks ($p < 0.0001$), and 5.54 ± 1.44 at 12 weeks ($p < 0.0001$) in PP. Mean SANDE was 67.69 ± 16.50 at baseline, 57.26 ± 19.50 at 4 weeks ($p < 0.0001$), 48.55 ± 22.41 at 8 weeks ($p < 0.0001$), and 42.40 ± 23.25 at 12 weeks ($p < 0.0001$) in FAS, and 68.10 ± 16.40 at baseline, 57.19 ± 20.36 at 4 weeks ($p < 0.0001$), 49.69 ± 22.52 at 8 weeks ($p < 0.0001$), and 43.71 ± 24.24 at 12 weeks ($p < 0.0001$) in FAS in PP. ODS was 17.30 ± 7.24 at baseline, 14.33 ± 6.53 at 4 weeks ($p < 0.0001$), 11.95 ± 6.48 at 8 weeks ($p < 0.0001$), and 10.43 ± 7.16 at 12 weeks ($p < 0.0001$) in FAS, and 17.27 ± 7.29 at baseline, 14.13 ± 6.88 at 4 weeks ($p < 0.0001$), 12.19 ± 6.37 at 8 weeks ($p < 0.0001$), and 10.49 ± 6.80 at 12 weeks ($p < 0.0001$) in PP. Tear volume was 2.81 ± 1.64 at baseline, 3.53 ± 2.46 at 4 weeks ($p < 0.05$), 3.81 ± 2.86 at 8 weeks ($p < 0.01$), and 3.71 ± 2.21 at 12 weeks ($p < 0.01$) in FAS, and 2.69 ± 1.41 at baseline, 3.41 ± 2.41 at 4 weeks ($p < 0.05$), 3.73 ± 2.53 at 8 weeks ($p < 0.01$), and 3.71 ± 2.34 at 12 weeks ($p < 0.001$) in PP (Fig. 4).

The improvement rate of SANDE represented 44 (48.89%) at 4 weeks, 69 (76.67%) at 8 weeks, and 73 (81.11%) at 12 weeks in FAS, and 36 (51.43%) at 4 weeks, 52 (74.29%) at 8 weeks, and 56 (80.00%) at 12 weeks in PP. There was a significant increase in both FAS and PP ($p < 0.0001$) (Fig. 5). PRO of 75 patients who had finished this clinical trial showed 4 much improvement (5.33%), 46 improvement (61.33%), 24 no change (32.00), 1 aggravation (1.33%), and no one much aggravation (0%). Discomforts in the use of 0.1% CsA were blurring (26, 34.67%), pain (16, 21.33%), foreign body sensation (14, 18.67%), irritation (10, 13.33%), and others (9, 12%). The mean medication compliance of 0.1% CsA was 95.57 ± 10.34 and there were two cases which showed compliance under 70%.

In the FAS, eleven of ninety patients had Sjögren's syndrome, and in the PP analysis, nine of seventy patients were diagnosed with Sjögren's syndrome. In the FAS, both groups showed significant decreases over 12 weeks in corneal and conjunctival staining scores ($p < 0.0001$, $p < 0.001$ respectively), but no significant differences were observed between the groups ($p = 0.60$, $p = 0.29$). The conjunctival staining score was significantly lower in the non-Sjögren's syndrome group ($p < 0.0001$). TF-BUT, mean SANDE, ODS, and tear volume all showed significant decreases over 12 weeks in both groups (all $p < 0.0001$), with no significant differences between two groups (all $p > 0.05$). However, the non-Sjögren's syndrome group exhibited significantly longer TF-BUT and lower SANDE scores compared to the Sjögren's syndrome group (Fig. 6). In the PP analysis, the corneal staining score significantly decreased over 12 weeks in both groups ($p < 0.0001$), with no significant differences between two groups ($p = 0.24$). There were also no significant differences between two groups ($p = 0.52$). The conjunctival staining score was significantly lower in the non-Sjögren's syndrome group than in the Sjögren's

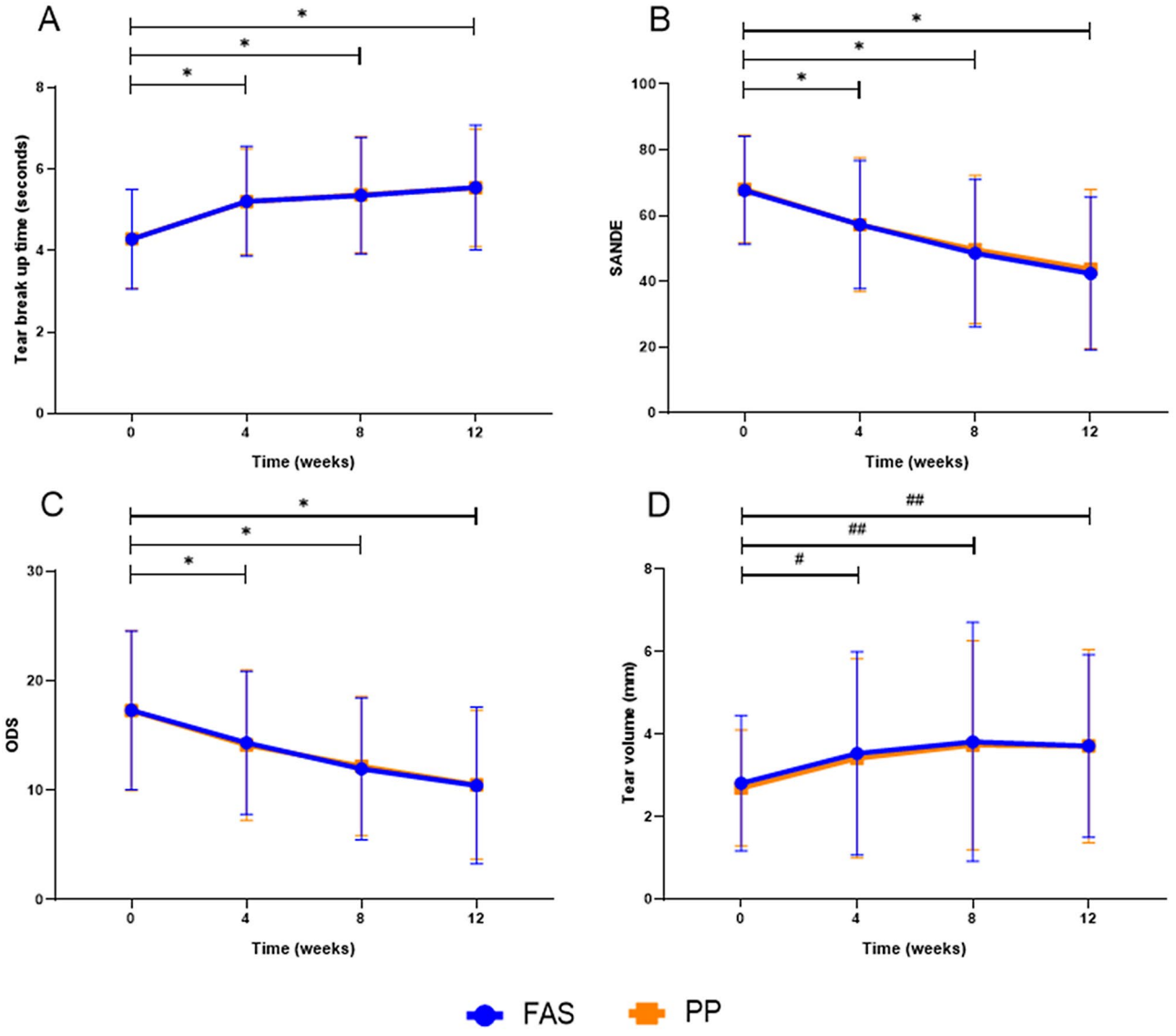

Fig. 4 Changes in the tear film break-up time, SANDE, ODS, and tear volume over 12 weeks after switching to 0.1% from 0.05% cyclosporine A in FAS and PP. **A**. Tear Film Break-up time (TF-BUT): All TF-BUT differences compared to baseline at each visit showed significant improvement (all $p < 0.0001$). The change by time showed significance (both $p < 0.0001$). **B**. SANDE (symptom assessment in dry eye): All SANDE differences compared to baseline at each visit showed significant improvement (all $p < 0.0001$). The change by time showed significance (both $p < 0.0001$). **C**. ODS (ocular discomfort scale): All ODS differences compared to baseline at each visit showed significant improvement (all $p < 0.0001$). The change by time showed significance (both $p < 0.0001$). **D**. Tear volume: All tear volume differences compared to baseline at each visit showed significant improvement (all $p < 0.05$). The change by time showed significance (both $p < 0.0001$). FAS: full analysis set, PP: per protocol set. *: $p < 0.0001$. #: $p < 0.05$, ##: $p < 0.01$

syndrome group ($p < 0.0001$), but there was no significant change over 12 weeks ($p = 0.06$). Furthermore, no significant differences were found between two groups ($p = 0.18$). TF-BUT, mean SANDE, and ODS all showed significant decreases over 12 weeks in both groups (all $p < 0.0001$), with no significant differences between two groups (all $p > 0.05$). The non-Sjögren's syndrome group had significantly longer TF-BUT, lower SANDE, and lower ODS scores than the Sjögren's syndrome group (all $p < 0.05$). However, tear volume showed no significant differences between two groups (all $p > 0.05$) (Fig. 7).

There was no significant difference of change in the corneal staining score ($p = 0.60$), conjunctival staining score ($p = 0.29$), TF-BUT ($p = 0.09$), SANDE ($p = 0.38$) ODS ($p = 0.9$), tear volume ($p = 0.66$) between non-Sjogren's syndrome patients (79 cases) and Sjogren's syndrome patients (11 cases) through the study. Moreover, there was no significant difference at each visit compared to baseline in all parameters (all $p > 0.05$).

Adverse effects were observed in 16 patients (23 cases) out of 90 patients. There were 7 cases of ocular symptoms associated with adverse events (AEs), of which pain after

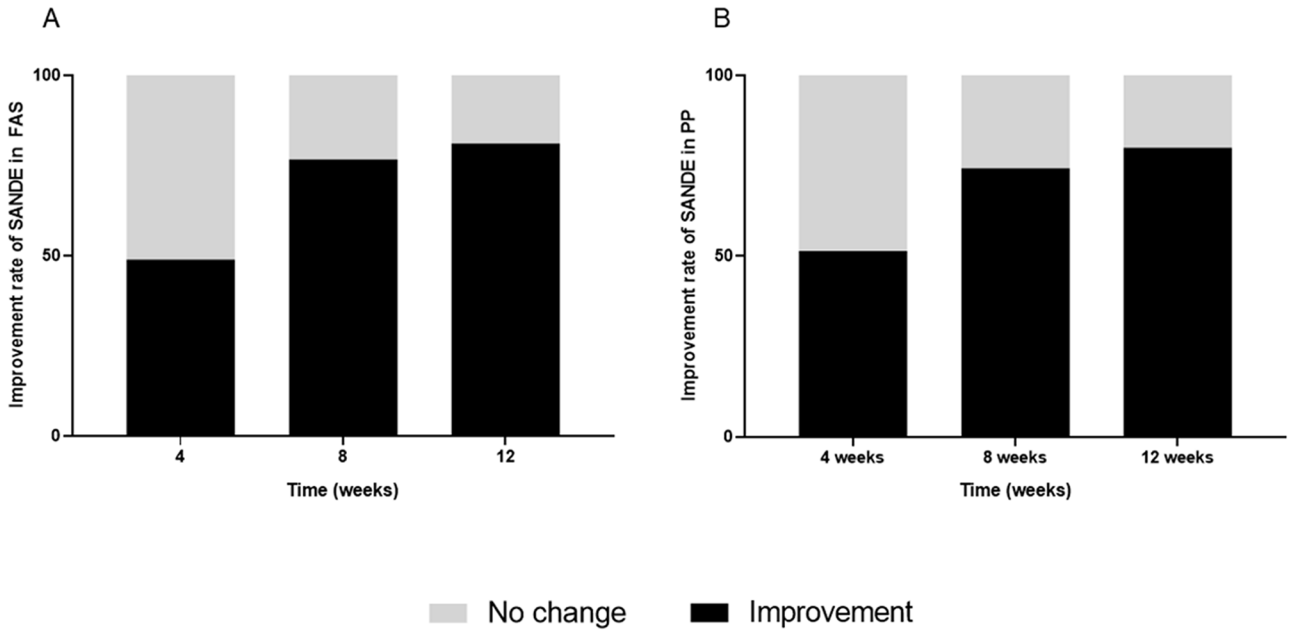

Fig. 5 The improvement rate of SANDE between each visit with baseline in FAS and PP. **A**. Improvement rate of SANDE in FAS: The change by time showed significance ($p < 0.0001$). **B**. Improvement rate of SANDE in PP: The change by time showed significance ($p < 0.0001$). SANDE = symptom assessment in dry eye. FAS: full analysis set, PP: per protocol set

instillation had a clear association. The remaining 22 cases were not relevant with the clinical trial. Most of the AEs were grade I (18 cases, 78.26% of all AEs) and grade II AE was seen in four patients (17.39%). A Grade III AE of mechanical ileus was reported in one patient. It was not associated with the clinical trial, and the patient has recovered. The information regarding AEs is provided in Supplement 2.

Discussion

Ocular surface inflammation is one of the key factor in DED [21]. The recent guidelines of Dry Eye Workshop (DEWS) II by the Tear Film and Ocular Surface Society (TFOS) recommend anti-inflammatory agents, such as corticosteroids, lifitegrast, oral tetracyclines, and CsA in DED [22]. As topical corticosteroids have possible complications like cataract, ocular hypertension, decreased wound healing, and risk of infection, the agent with less complications are required for long term use [23]. Since 2003, an early model of 0.05% CsA has shown a good performance to control the symptoms and signs of DED [23] and reduce level of histocompatibility human leukocyte antigen-DR isotype gene (HLA-DR) which represent the grade of inflammation on epithelial cells [24].

However, a group of patients with moderate to severe DED have inadequate clinical responses to twice-daily instillation of 0.05% CsA. Insufficient dosing, low concentration to target cells or tissues and unresponsiveness to ocular surface specific immunologic mechanisms may explain this inadequate responsiveness [13].

To overcome the inadequate efficacy of 0.05% CsA, several methods such as frequent instillation or formulation change have been studied [25, 26]. There is close relationship between systemic CsA concentration and its immunosuppressive potency, and frequent dosing of 0.05% CsA showed the clinical improvement in patients with severe inflammatory DED. However, the regimen can reduce patient compliance and it leads to inadequate results [27].

0.1% CsA CE has higher drug concentration than conventional CsA and showed the higher conjunctival drug concentrations in rabbit eyes for its electrostatic interactions between the positively charged droplets and negatively charged mucin proteins of ocular surface [28]. With this drug characteristics, 0.1% CsA CE was presented and it showed potent clinical efficacy in various ocular surface diseases, including DED [11, 17, 29, 30]. However, there has been no study on the superiority of 0.1% CsA over 0.05% CsA in the treatment of DED. In this study, we aimed to evaluate the switching efficacy to 0.1% CsA CE from conventional 0.05% CsA anionic emulsion in patients with moderate to severe DED.

After switching to 0.1% CsA, objective signs including NEI score, TF-BUT and tear volume were

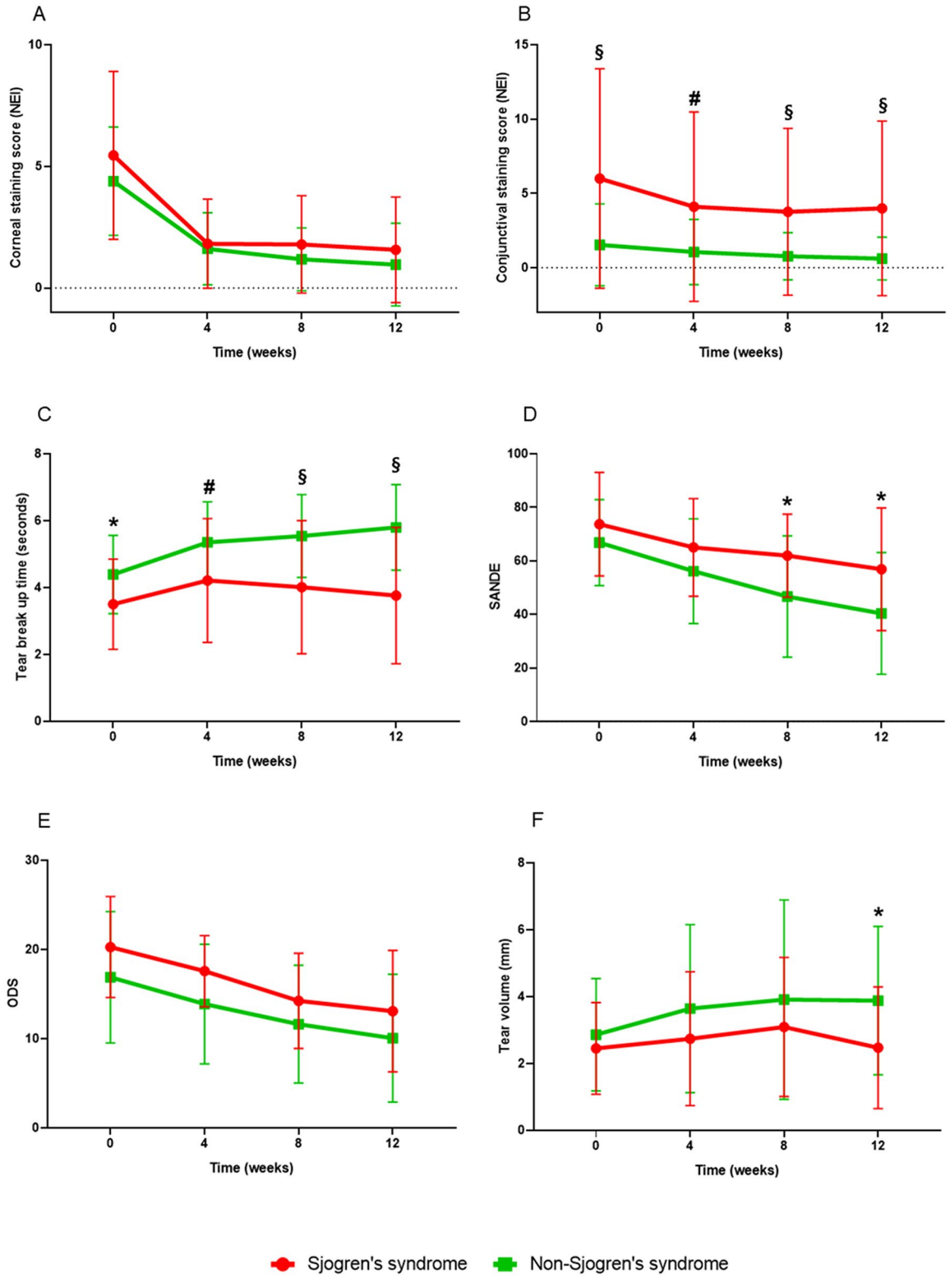

Fig. 6 (See legend on next page.)

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Fig. 6 Subgroup analysis between Sjogren's syndrome and non-Sjogren's syndrome in FAS. **A**. Corneal staining score: Change pattern by time was no significant difference between two group ($p = 0.60$). Change by time was significant ($p < 0.0001$). **B**. Conjunctival staining score: Change pattern by time was no significant difference between two group ($p = 0.60$). Change by time was significant ($p < 0.0001$). There were significant differences between two groups at baseline, 4, 8, 12 weeks. **C**. Tear Film Break-up time (TF-BUT): Change pattern by time was no significant difference between two group ($p = 0.08$). Change by time was significant ($p < 0.0001$). There were significant differences between two groups at baseline, 4, 8, 12 weeks. **D**. SANDE (symptom assessment in dry eye): Change pattern by time was no significant difference between two group ($p = 0.08$). Change by time was significant ($p < 0.0001$). There were significant differences between two groups at 8, 12 weeks. **E**. ODS (ocular discomfort scale): Change pattern by time was no significant difference between two group ($p = 0.91$). Change by time was significant ($p < 0.0001$). **F**. Tear volume: Change pattern by time was no significant difference between two group ($p = 0.91$). Change by time was significant ($p < 0.0001$). There were significant differences between two groups at 12 weeks. FAS: full analysis set. *: $p < 0.05$, #: $p < 0.01$, §: $p < 0.001$

improved, SANDE and ODS scores also was decreased. We enrolled Sjögren's syndrome patients who demonstrated inadequate responses to 0.05% CsA and performed subgroup analyses for both the Sjögren's and non-Sjögren's groups. While the conjunctival staining score, TF-BUT, SANDE in Sjögren's syndrome was significantly severe than non-Sjögren's syndrome in FAS, Sjögren's syndrome group showed similar change patterns to non-Sjögren's syndrome over 12 weeks. According to SICCANOVE and SANSIKA study, 0.1% CsA CE presented a clinical efficacy against the vehicle control group [11, 12]. Two studies included Sjogren syndrome cases and both the corneal staining score and OSDI were improved in the treatment group with 0.1% CsA. Kim et al. reported a higher efficacy by switching to 0.1% CsA CE (Ikervis) from 0.05% CsA (Restasis) in patients with Sjogren syndrome [19]. Forty patients with an ocular surface staining score of more than 4 (Sjogren's International Collaborative Clinical Alliance, SICCA) showed significant improvements than those with a staining score of under 4 after switching. Likewise, this study also demonstrated the efficacy of switching to 0.1% CsA CE in the Sjögren's group, which was comparable to the effects observed in the non-Sjögren's subgroup, despite the more severe disease severity in the Sjögren's group.

Topical CsA has an issue about ocular discomfort after instillation which had been reported in various clinical trials. In our study, patients who experienced ocular pain and discomfort after using 0.1% CsA CE were reported in 16 and 14 of 75 cases (21.33% and 18.67%). Of the 20 dropout participants, 2 discontinued the clinical trial due to pain after instillation of the test drug. Considering the relatively small number of dropouts compared to the number of participants experiencing discomfort after eyedrop administration, it can be inferred that the medication adherence is relatively high. According to a meta-ananalysis, pain after instillation was consistently reported in studies of topical CsA, regardless of the concentration and formulation used [10]. The correlation between the discomfort and CsA concentration or formulation remains unclear. Although the discomfort has been issued in this trial, there has not observed any clinically significant side effects of 0.1% CsA CE. Therefore, long-term safety was also demonstrated during the study period.

0.1% CsA CE is formulated as a cationic emulsion due to the lipophilicity and poor water solubility of CsA [31]. In contrast to the anionic emulsion, the CE formula has been reported to stabilized the tear film lipid layer of the ocular surface [32]. Consequently, although the increased concentration in this study might have contributed to its efficacy, the benefits derived from the formulation itself should also be considered.

This study aimed to determine the additional effects that could be obtained by replacing the insufficient effect of 0.05% CsA with 0.1% CsA CE. Therefore, artificial tears or diquafosol eyedrops that were previously used were maintained, and the patients were instructed to continue using their usual medications without change. Therefore, this study had an advantage to find the direct effect of switching based on these reasons. However, this strategy of the study has a limitation that different reactivity to 0.1% CsA CE may vary across patients because the eye drops or systemic drugs used by the patients were not identical. And open label design was another major limitation of this study. A double-blinded, randomized clinical trial should be considered to evaluate the efficacy and safety of 0.1% CsA CE, but it has the disadvantages of being difficult to have a washout period and conducting a long-term study when targeting moderate to severe DED patients. Therefore, we designed switching clinical trial, and it proved the additional effect of 0.1% CsA CE. Despite of these limitations, this study demonstrated the effectiveness of 0.1% CsA CE in the patients who had inadequate effects by treatment with 0.05% CsA with DED. In the clinical setting, the choice of drug is very important because patients have different drug responses. In patients who are less responsive to the safe 0.05% CsA we use, we recommend switching to 0.1% CsA CE.

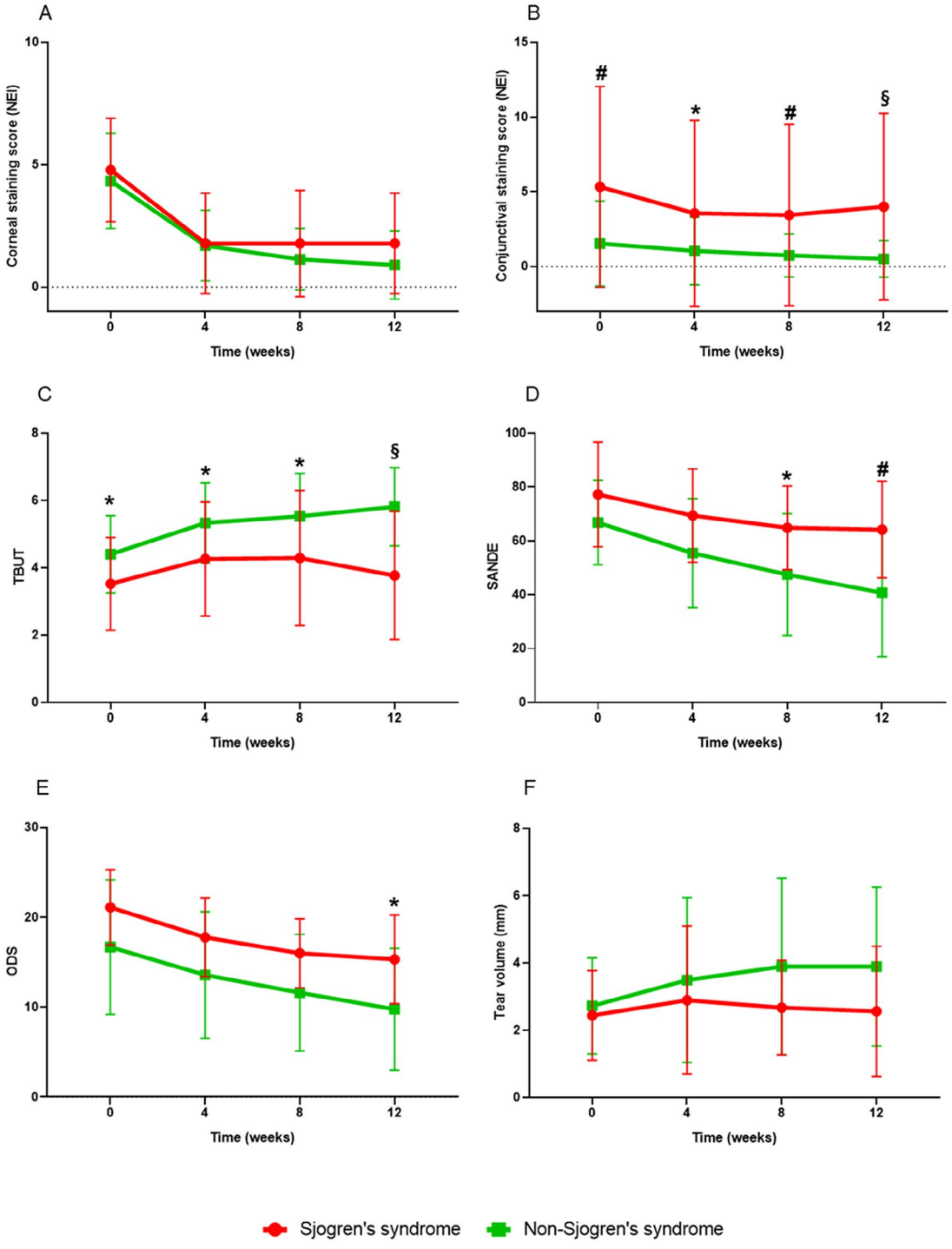

Fig. 7 Subgroup analysis between Sjogren's syndrome and non-Sjogren's syndrome in PP. **A**. Corneal staining score: Change pattern by time was no significant difference between two group ($p = 0.52$). Change by time was significant ($p < 0.0001$). **B**. Conjunctival staining score: Change pattern by time was no significant difference between two group ($p = 0.18$). Change by time had no significance ($p = 0.06$). There were significant differences between two groups at baseline, 4, 8, 12 weeks. **C**. Tear Film Break-up time (TF-BUT): Change pattern by time was no significant difference between two group ($p = 0.06$). Change by time was significant ($p < 0.0001$). There were significant differences between two groups at baseline, 4, 8, 12 weeks. **D**. SANDE (symptom assessment in dry eye): Change pattern by time was no significant difference between two group ($p = 0.14$). Change by time was significant ($p < 0.0001$). There were significant differences between two groups at 8, 12 weeks. **E**. ODS (ocular discomfort scale): Change pattern by time was no significant difference between two group ($p = 0.80$). Change by time was significant ($p < 0.0001$). There were significant differences between two groups at 12 weeks. **F**. Tear volume: Change pattern by time was no significant difference between two group ($p = 0.52$). Change by time had no significance ($p = 0.27$). PP: per protocol set. *: $p < 0.05$, #: $p < 0.01$, §: $p < 0.001$

Supplementary Information

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Supplementary Material 1

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Author contributions
S.H.Y.: Writing - Data Curation, Original Draft, Investigation. E.C.K.: Conceptualization, Investigation. I.C.Y.: Methodology, Investigation. C.Y.C.: Validation, Investigation. J.Y.K.: Investigation, Resources. J.S.S.: Methodology, Investigation. J.Y.H.: Conceptualization, Investigation. H.K.K.: Conceptualization, Writing - Review & Editing. K.Y.S.: Conceptualization, Supervision, Visualization.

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Data availability
The datasets generated during and / or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All patients who were enrolled provided written informed consent, and the study was conducted in accordance with the tenets of the Declaration of Helsinki with an approval from the Institutional Review Boards of the Yonsei University College of Medicine (4-2019-1156).

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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References

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276–83.
2. Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15(3):438–510.
3. Baudouin C. [A new approach for better comprehension of diseases of the ocular surface]. J Fr Ophtalmol. 2007;30(3):239–46.
4. Knop E, Knop N, Brewitt H. [Dry eye disease as a complex dysregulation of the functional anatomy of the ocular surface. New concepts for understanding dry eye disease]. Ophthalmologe. 2003;100(11):917–28.
5. De Paiva CS, Pangelinan SB, Chang E, et al. Essential role for c-Jun N-terminal kinase 2 in corneal epithelial response to desiccating stress. Arch Ophthalmol. 2009;127(12):1625–31.
6. Okanobo A, Chauhan SK, Dastjerdi MH, et al. Efficacy of topical blockade of interleukin-1 in experimental dry eye disease. Am J Ophthalmol. 2012;154(1):63–71.
7. De La Maza Serra S, Simon Castellvi M, Kabbani C. [Nonpreserved topical steroids and lacrimal punctal occlusion for severe keratoconjunctivitis sicca]. Arch Soc Esp Oftalmol. 2000;75(11):751–6.
8. Bushley KE, Raja R, Jaiswal P, et al. The genome of tolypocladium inflatum: evolution, organization, and expression of the cyclosporin biosynthetic gene cluster. PLoS Genet. 2013;9(6):e1003496.
9. Pleyer U, Geerling G, Schrader S, et al. [If Artificial tears aren't enough. The importance of inflammatory processes in Dry Eye Disease. Practical aspects of an anti-inflammatory therapy of Dry Eye Disease]. Klin Monbl Augenheilkd. 2020;237(5):655–68.
10. de Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine A therapy for dry eye syndrome. Cochrane Database Syst Rev. 2019;9(9):CD010051.
11. Leonardi A, Van Setten G, Amrane M, 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(4):287–96.
12. Baudouin C, Figueiredo FC, Messmer EM, 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(5):520–30.
13. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group Ophthalmol. 2000;107(4):631–9.
14. Jerkins GW, Pattar GR, Kannarr SR. A review of topical cyclosporine a Formulations-A Disease-Modifying Agent for Keratoconjunctivitis Sicca. Clin Ophthalmol. 2020;14:481–9.
15. Peng W, Jiang X, Zhu L, et al. Cyclosporine A (0.05%) Ophthalmic Gel in the treatment of Dry Eye Disease: a Multicenter, Randomized, Double-Masked, phase III, COSMO Trial. Drug Des Devel Ther. 2022;16:3183–94.
16. Daull P, Lallemand F, Garrigue JS. Benefits of cetalkonium chloride cationic oil-in-water nanoemulsions for topical ophthalmic drug delivery. J Pharm Pharmacol. 2014;66(4):531–41.
17. Baudouin C, de la Maza MS, Amrane M, et al. One-year efficacy and safety of 0.1% cyclosporine a Cationic Emulsion in the treatment of severe Dry Eye Disease. Eur J Ophthalmol. 2017;27(6):678–85.
18. Pisella PJ, Labetoulle M, Doan S, 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.
19. Kim J, Moon TK, Yoon HJ, et al. Efficacy of switching from Cyclosporine A 0.05% Anionic Emulsion to Cyclosporine A 0.1% Cationic Emulsion in patients with Dry Eye Associated with Sjogren's syndrome. J Ocul Pharmacol Ther. 2021;37(8):472–8.
20. Hao Y, Tian L, Cao K, Jie Y. Repeatability and reproducibility of SMTube Measurement in Dry Eye Disease patients. J Ophthalmol. 2021;2021:1589378.
21. Stern ME, Pflugfelder SC. Inflammation in dry eye. Ocul Surf. 2004;2(2):124–30.
22. Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. Ocul Surf. 2017;15(3):575–628.
23. McGhee CN, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids: benefits and risks. Drug Saf. 2002;25(1):33–55.
24. Kunert KS, Tisdale AS, Stern ME, et al. Analysis of topical cyclosporine treatment of patients with dry eye syndrome: effect on conjunctival lymphocytes. Arch Ophthalmol. 2000;118(11):1489–96.
25. Dastjerdi MH, Hamrah P, Dana R. High-frequency topical cyclosporine 0.05% in the treatment of severe dry eye refractory to twice-daily regimen. Cornea. 2009;28(10):1091–6.
26. Byun YS, Rho CR, Cho K, et al. Cyclosporine 0.05% ophthalmic emulsion for dry eye in Korea: a prospective, multicenter, open-label, surveillance study. Korean J Ophthalmol. 2011;25(6):369–74.
27. Babany G, Morris RE, Babany I, Kates RE. Evaluation of the in vivo dose-response relationship of immunosuppressive drugs using a mouse heart transplant model: application to cyclosporine. J Pharmacol Exp Ther. 1988;244(1):259–62.

28. Daull P, Lallemand F, Philips B, et al. Distribution of cyclosporine A in ocular tissues after topical administration of cyclosporine a cationic emulsions to pigmented rabbits. Cornea. 2013;32(3):345–54.
29. 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(5):671–81.
30. Deshmukh R, Ting DSJ, Elsahn A, et al. Real-world experience of using cyclosporin-A 0.1% in the management of ocular surface inflammatory diseases. Br J Ophthalmol. 2022;106(8):1087–92.
31. Fahr A. Cyclosporin clinical pharmacokinetics. Clin Pharmacokinet. 1993;24(6):472–95.
32. Daull P, Amrane M, Ismail D, 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(6):355–65.

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