Long-term Results of Topical 0.02% Tacrolimus Ointment for Refractory Ocular Surface Inflammation in Pediatric Patients

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Research Article

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Abstract

Background: To investigate the efficacy and safety of long-term treatment with topical 0.02 % tacrolimus ointment for ocular inflammation in pediatric patients. No studies have been reported on the outcome of long-term (≥12 months) use of topical tacrolimus in pediatric patients for treatment of ocular surface diseases.

Methods: A total of 144 eyes of 72 pediatric patients who were prescribed topical 0.02% tacrolimus ointment between January of 2010 and March of 2018 for anterior segment inflammatory disorders refractory to conventional steroid therapy were included. Patients completed questionnaires and underwent slit-lamp examinations for evaluation of symptoms and signs at baseline. Patients were followed 1, 2, 3, 6, 9 and 12 months after initiation of tacrolimus treatment. After 12 months, patients were followed every 3 months for monitoring of possible adverse events and clinical outcomes. Changes in ocular surface parameters during slit-lamp examination, clinical symptoms and concurrent steroid use were graded with a scoring system. The presence of side effects was also verified.

Results: Among 72 patients (56 % males, age 10.79 ± 3.96 years), 25 patients (48% males, age 11.42 ± 3.91 years) fully recovered, resulting in discontinuance of the ointment treatment before 12 months. Six patients experienced intolerable burning sensation, which required treatment cessation. Cessation days of those who quit were 1,5,14,20,26, and 35 days. Seven patients were lost during follow-up. Thirty-four patients (56% males, age 11.20 ± 4.21 years) were treated with tacrolimus ointment for over 12 months (average 23.12 ± 19.07 months). During the follow-up period, all patients showed improved clinical signs and symptoms, and no adverse reaction was noted.

Conclusions: Long-term maintenance of topical tacrolimus 0.02% ointment is safe and effective in improving refractory ocular surface inflammatory diseases in pediatric patients.

Background

The inflammatory anterior segment disease management requires intense immunosuppression [1]. Topical steroids are currently the mainstay treatment. However, prolonged steroid use can potentially cause severe adverse reactions, including steroid-induced glaucoma (SIG), posterior subcapsular cataract, and secondary infection [2]. Pediatric patients, in particular, tend to show a more severe response to topical steroids compared to adults [2, 3]. In one study involving 1,259 children with glaucoma, 4.7% were cases of SIG. Of these patients, 87% had been prescribed with topical steroids for vernal keratoconjunctivitis (VKC) [2].

To overcome the limitations of steroids, topical immunosuppressants have been proposed as an alternative. Tacrolimus is a nonsteroidal macrolide immunosuppressant isolated from *Streptomyces tsukubaensis* and is known to be 30 ~ 100 times more powerful than cyclosporine [4]. The mechanism by which tacrolimus suppresses inflammatory reactions is not clear. So far, it has been discovered that tacrolimus attaches to FK506-binding proteins within T lymphocytes and suppresses calcineurin activity

[5]. Calcineurin is thought to be necessary for T-cell activation [6]. Subsequent inhibition of T lymphocytes results in the inhibition of release of inflammatory cytokines [1], including IL-2 from T lymphocytes [7]. Tacrolimus also inhibits histamine release from mast cells and may alleviate allergic symptoms through similar mechanisms [8].

Many studies have described satisfactory results with topical tacrolimus on various ocular surface inflammatory diseases [1, 9, 10]. However, no studies to date have investigated the safety of long-term (≥ 12 months) use of topical tacrolimus in pediatric patients for the purpose of treating ocular surface diseases. The goal of this paper was to examine the efficacy and safety of long-term treatment using topical 0.02% tacrolimus ointment in pediatric patients with ocular surface inflammation refractory to conventional therapy.

Methods

This study was conducted at the Department of Ophthalmology, Severance Hospital, Yonsei University. The study protocol was approved by the Institutional Review Board of Yonsei University, Seoul, Korea (IRB number: 4-2019-1315), and it adhered to the tenets of the Declaration of Helsinki. The written informed consent was waived because of the retrospective design and the use of deidentified patient data. We retrospectively reviewed the medical records of 72 consecutive patients diagnosed with inflammatory conditions such as such as ocular Graft-versus-host disease (GVHD), VKC, atopic keratoconjunctivitis (AKC), ocular cicatricial pemphigoid (OCP), Stevens–Johnson syndrome (SJS), and phlyctenular keratoconjunctivitis (PKC) under 18 years (mean age, 10.79 years; range, 3 ~ 17 years) of age. The patients had been prescribed with topical 0.02% tacrolimus ointment at the ophthalmology clinic from January 2010 to March 2018. Exclusion criteria were history of contact lens usage, previous ocular trauma, past ocular surgery, and known allergic reaction to tacrolimus. All patients had a history of moderate to severe disease necessitating frequent (more than six times/day) or continuous (for more than 3 months) use of topical steroid therapy to control intractable inflammation. We defined the cases showed aggressive, worsening inflammation progression despite receiving a steroid treatment for more than 2 weeks, cases in which there was a relapse after tapering or withdrawal of steroids, and cases in which steroid-related complications developed as “refractory to conventional treatment.” The “refractory to conventional treatment” patients were prescribed with topical 0.02% tacrolimus ointment as an adjunct immunosuppressive therapy in addition to previous steroid treatments to get clinical improvement [9].

During initial visit, all patients were asked to complete a questionnaire to evaluate subjective symptoms. They also underwent slit-lamp examination. The subjects were instructed not to use any eyedrops for 2 hours prior to the examinations. The disease severity was classified as absent, mild, moderate, or severe according to a grading system out of four points based on symptoms and signs (Table 1) [11]. Clinical outcomes were assessed using the same grading system. The presence of adverse reaction was identified to evaluate the safety. The objective signs and safety were observed at initial visit and 1, 2, 3, 6, 9, and 12 months after initiation of the tacrolimus eye drop treatment. After 12 months, the patient was followed-up every 3 months. The slit-lamp examinations were conducted by a single clinician (K.Y.S.) for

consistency. The changes in disease severity and patient symptoms were compared between baseline and after the treatment.

Table 1 Grading system of disease severity

Symptoms and severity	Score	Clinical signs and severity	Score
Discharge		Conjunctival fibrosis	
Absent	0	No scar	0
Mucoid discharge in the lower cul-de-sac	1	Subepithelial fibrosis	1
Moderate	2	Fornix shortening	2
Matted lids requiring frequent cleaning	3	Symblepharon	3
Itching		Conjunctival hyperemia	
No need to itch	0	Absent	0
Occasional itching	1	Dilation of some blood vessels (1 quadrant)	1
Frequent itching	2	Dilation of several blood vessels (<1 quadrant)	2
Constant itching	3	Generalized dilation of blood vessels	3
Photophobia		Limbal inflammation	
Absent	0	None	0
Sensitivity to sunlight but can open eyes	1	1 quadrant	1
Eyes cannot be kept open for long to sunlight	2	2 quadrants	2
Avoidance sunlight and inability to open eyes	3	3-4 quadrants	3
Perceived redness		Punctate keratopathy	
Absent	0	Intact epithelium	0
Detected only on close observation	1	Punctate in 1/3 of cornea	1
Detectable at near	2	Punctate in 2/3 of cornea	2
Detectable at distance	3	Diffuse punctate	3

The use of steroid was categorized and scored on a scale of 0 to 4. The score of 0 indicates no steroid necessary; 1 indicates the use of 0.1% topical fluorometholone (Ocumetholone®; Samil Pharmaceutical Co., Ltd., Seoul, Korea); 2 indicates the use of 0.12% topical prednisone acetate (Optilon®; Chong Kun Dang Pharmaceutical Co., Seoul, Korea); 3 indicates the use of 1% topical prednisone acetate (Predforte®; Allergan Inc., Irvine, CA, USA) or 1% rimexolone (Vexol®; Alcon Laboratories Inc., Fort Worth, TX, USA); and 4 indicates the use of systemic steroids with or without concurrent topical prednisone acetate of 1% [6, 9].

When directly applied to the eye, the tacrolimus ointment (Protopic ointment 0.03%; Astellas Pharma, Tokyo, Japan), which has been used to treat dermatologic disorders, causes severe adverse effects. In order to allow for long-term use of the ointment for eye diseases, we have diluted the ointment to 0.02% by mixing the 0.03% tacrolimus ointment with a less viscous, 30 mg anhydros liquid lanolin with mineral oil base (Duratears; Alcon Laboratories, Inc., Fort Worth, Texas, USA) at a 2:1 ratio. When mixed together, Duratears® forms a layer that holds moisture [9]. The patients were instructed to put into the conjunctival sac mixed ointment about the size of a rice grain twice a day.

All continuous data are expressed as mean ± standard deviation (SD) while categorical data were presented as number and percentage of the total population. Statistical analyses were performed with the SPSS statistical software package (version 20.0; SPSS Inc, Chicago, Illinois, USA). A p-value less than 0.05 was considered statistically significant.

Results

We enrolled 144 eyes of 72 patients who were treated with the topical 0.02% tacrolimus ointment for “refractory to conventional treatment” ocular surface diseases. All patients had bilateral ocular involvement. Seven patients were lost during follow-up. Six of 65 patients experienced painful burning sensation and withdrew from the tacrolimus treatment. The number of days before the cessation of treatment due to severe burning sensation was 1, 5, 14, 20, 26, and 35 days (Fig. 1). No side effects other than burning sensation were identified. Twenty-five of 65 patients fully recovered, resulting in discontinuation of the tacrolimus ointment before 12 months. Thirty-four patients (68 eyes) were treated with tacrolimus ointment for 12 months or more (total treatment duration 23.12 ± 19.07 months). The demographics of 34 patients who were followed for longer than 12 months are listed in detail in Table 2. The average age was 11.20 ± 4.21 (range, 3 to 17) years. The subjects included 19 (56%) males and 15 (44%) females. The average follow-up period was 23.12 ± 19.07 months (range 12 to 98 months). The distribution of diagnosis of 65 patients (seven patients lost to follow-up were excluded) is shown in Table 3. The most common condition was AKC (46%), followed by VKC (35%), GVHD (15%) and PKC (3%). SJS and OCP each accounted for 1%.

Table 2
Demographic features of pediatric patients treated with tacrolimus ointment over 12 months

	Value
Age (years), mean ± SD	11.20 ± 4.21 (range, 3 to 17)
Gender (M : F)	19 : 15
Follow-up period (months)	23.12 ± 9.07 (range, 12 to 98)

Table 3 Distribution of diagnosis of overall pediatric patients

Diagnosis	AKC	GVHD	VKC	PKC	SJS	OCP
Ratio(%)	46% (30)	13% (9)	34% (22)	3% (2)	2% (1)	2% (1)

AKC : Atopic keratoconjunctivitis
GVHD : Graft-versus-host disease
VKC : Vernal keratoconjunctivitis
PKC : Phlyctenular keratoconjunctivitis
OCP : Ocular cicatricial pemphigoid
SJS : Stevens-Johnson syndrome

In the AKC patient group, 14 of 32 patients fully recovered before 12 months and ceased the tacrolimus treatment. Three of 32 patients experienced painful burning sensation, which required treatment cessation. The number of days to cessation for those who quit because of severe burning sensation was

1, 14, and 35 days. Two patients were lost to follow-up. Thirteen patients were treated with tacrolimus ointment for 12 months or more. In the GVHD patient group, two of 11 patients were lost to follow-up. Nine patients were treated with tacrolimus ointment for 12 months or more. In the VKC patient group, 11 of 25 patients fully recovered, resulting in discontinuation of the ointment treatment before 12 months. Three of 32 patients experienced painful burning sensation and the treatment was withheld. The number of days before cessation because of severe burning sensation was 5, 20, and 26 days. Three patients were lost to follow-up. Eight patients were treated with tacrolimus ointment for 12 months or more. All of PKC, OCP, and SJS patients used tacrolimus ointment for more than 12 consecutive months.

Comparisons of ocular examination results between before and after the treatment of 34 patients with a follow-up period of 12 months or longer showed no significant difference in the mean IOP (14.82 ± 3.63 vs 15.26 ± 2.57, P = 0.419) and visual acuity (0.22 ± 0.31 vs 0.18 ± 0.30, P = 0.199). The overall severity of disease was assessed by the sum of symptom and sign scores. The mean composite sign score at initial visit was 9.44 ± 2.11 and dropped to 2.85 ± 1.37 at 12 months ($P < .001$). The mean composite symptom score at initial visit was 7.35 ± 1.85 and dropped to 2.17 ± 1.08 at 12 months ($P < .001$). The changes in mean scores for the symptoms and signs during follow-up are demonstrated in Fig. 2. After 4 weeks of treatment, significant improvement in symptoms and signs was noted (Fig. 2). The total sign score (range, 0–12) significantly decreased 4 weeks after initiation of topical tacrolimus ointment in all disease groups (Fig. 3-a). The total symptom score (range, 0–12) also showed a significant decrease from baseline 4 weeks after initiation of topical tacrolimus ointment in all disease groups (Fig. 3-b). There were no corneal deposits, ocular surface staining, IOP elevation, infections, or other unfavorable influences associated with the instillation of topical tacrolimus ointment during the follow-up period.

In line with the improvement of the patient's sign and symptom, we tried tapering oral and topical steroid or changing to a topical steroid with lower pharmacologic efficacy. During the follow-up, the percentage of eyes receiving adjunctive topical steroid treatment decreased to 82% at 2 months and 47% at 6 months. The percentage of eyes with adjunctive 1% prednisone was 41%, 29%, and 6% at 1, 2, and 6 months, respectively. The percentage of eyes with adjunctive 0.1% fluorometholone eye drops was 32%, 29%, and 24% at 1, 2, and 6 months, respectively. More than half of the total patients were treated with tacrolimus alone, successfully weaned off topical steroids at 6 months. (Fig. 4). The steroid score improved significantly from 3.32 ± 0.84 at baseline to 0.58 ± 0.65 at the final follow-up (Table 4). Reducing steroid use helped lower side effects associated with steroid use, such as glaucoma, cataract, and infection.

Table 4
Before and after treatment comparison of parameters associated with therapeutic effects

Variable	Before treatment	Final follow-up	*P*-value
BCVA (logMAR, mean ± SD)	0.22 ± 0.31	0.18 ± 0.30	0.199[a]
IOP, mmHg (mean ± SD)	14.82 ± 3.63	15.26 ± 2.57	0.419[a]
Symptom Score	7.35 ± 1.85	1.23 ± 0.95	0.001[b]*
Sign Score	9.44 ± 2.11	1.71 ± 1.06	0.001[b]*
Steroid Score	3.32 ± 0.84	0.58 ± 0.65	0.001[b]*
BCVA, best corrected visual acuity; SD, standard deviation; IOP, intraocular pressure.			
[a]Paired-t test; [b]Wilcoxon signed rank test.			
**P* < 0.05 was considered statistically significant.			

Discussion

The current study investigated the long-term safety of topical tacrolimus treatment in pediatric patients with inflammatory ocular surface disease that was refractory to conventional treatment. The results of our analyses showed that majority of patients tolerated the treatment, showed improved symptoms and clinical signs, and required less concurrent steroid therapy. Over 12 months of follow-up, no adverse reaction was noted.

The largest study to date to have investigated topical tacrolimus use in pediatric patients included only 45 patients. However, this study had limited the patient population to those diagnosed with VKC and the follow-up period was on average 8 months [12]. In contrast, our study included patients with follow-up period of 12 months or longer, where the average follow-up period reached 23.12 ± 19.07 (range, 12 to 98) months. In addition to VKC, this study included a variety of severe disease, such as GVHD, OCP, SJS, AKC, and PKC.

The absence of serious side effects in pediatric patients during the study period of 12 months emphasizes the safety of the prolonged use of the topical 0.02% tacrolimus ointment. Irritation upon application with complaints of transient burning sensation was the only side effect noted and the sole reason for treatment termination in six patients. No case of keratitis, IOP elevation, and infection related to topical tacrolimus was reported. These results suggest topical tacrolimus ointment as an efficient and safe treatment choice for ocular surface inflammation in pediatric patients.

The application of topical tacrolimus is effective in treating various T-cell-mediated ocular diseases [1]. T helper 2 (Th2) cells play a vital role in the pathogenesis of VKC. The Th2-derived cytokines such as

interleukin (IL)-3, IL-4, IL-5 and IL-13 are found to be increased in patients with the disease [13]. In AKC, both Th1 and Th2 cytokines are expressed in the irritated conjunctiva with possible Th1-mediated mechanisms [14]. Chronic ocular GVHD occurs in the near half of transplant recipients after hematopoietic stem cell transplantation. The inflammatory processes by reactive T cell of the lacrimal gland and ocular surface are thought to play vital roles in its pathogenesis [15]. OCP is a type of progressive cicatrizing conjunctivitis that results in fornix foreshortening and symblepharon [16]. By secreting cytokines that stimulate fibroplasia, T cells in conjunction with other forms of inflammatory cells are responsible for producing conjunctival scarring [1]. SJS lesions are produced by the migration of skin-homing cytotoxic T lymphocytes that release cytotoxic proteins to stimulate keratinocyte apoptosis [17]. PKC is an ocular immunological disorder, characterized by an allergic response in the conjunctiva and/or cornea [18, 19]. The pathogenesis of PKC is delayed-type hypersensitivity to foreign microbial proteins [20].

Tacrolimus is an effective steroid-sparing agent. While both steroids and tacrolimus inhibit inflammatory cells, tacrolimus is believed to be approximately 100 times more powerful than betamethasone valerate at inhibiting human epidermal Langerhans cell stimulatory function [21]. In the current study, patients were initially prescribed 0.02% tacrolimus ointment in combination with topical steroids during the active phase because topical tacrolimus requires several weeks to reach the treatment concentration in eyes. On the other hand, topical steroids are fast-acting and promptly relieve symptoms [22–24]. Therefore, topical steroids help resolve inflammation in the cornea and conjunctiva immediately until tacrolimus becomes effective.

Tacrolimus is hydrophobic. Therefore, in theory, the drug should permeate conjunctiva better than cornea because conjunctiva is more permeable to lipophilic drugs compared to cornea. This characteristic of tacrolimus may explain the higher efficacy of tacrolimus in patients with ocular GVHD with severe conjunctival inflammation [25].

The major side effects of topical tacrolimus are eye irritation, blurring, itching, chemosis, transient burning sensation, conjunctival hyperemia, and conjunctival chemosis [17]. Burning sensation, which was the reason behind treatment cessation in our study population, has been documented in previously published reports using higher concentrations (0.01%) but not in those using lower concentrations (0.005%). Hence, it is possible that this side effect is dependent on the drug concentration [17, 26, 27]. In terms of adverse effects, renal toxicity, hyperglycemia, and hypertension have been reported [28]. However, because of the limited amount of tacrolimus used during topical treatment, the risk of these adverse effects is negligible. A study that investigated the blood concentration profile of tacrolimus following topical application, its systemic exposure was reported to be minimal and temporary [29]. There have also been reports of complications such as blood dyscrasias, malignancies and outbreaks of infection including herpes simplex as well as organ damage with the use of tacrolimus. Such complications are thought occur more frequently in children, but no systemic complications were noted in our study. to be greater in children. A possible local adverse effect of topical tacrolimus is an increased predisposition to infections [24]. A study has shown that its long-term usage increases the risk of corneal

infections [27]. The prevalence of corneal infections in a large cohort of patients treated with topical tacrolimus was 0.35% [17]. However, no ocular complications were observed during our study.

The study has several limitations. The majority of patients (80%) were diagnosed with VKC and AKC patients. And because of that, the number of patients who finally maintained treatment for more than 12 months was relatively small. Although no major complications arose from the continuous use of topical tacrolimus for more than 12 months in pediatric patients in our study, adverse reactions might have been observed with a larger number of subjects. Despite these limitations, however, we believe that our long-term observation proved tacrolimus as an effective and safe treatment option in pediatric patients with inflammatory ocular surface disease.

Conclusions

Long-term treatment of topical tacrolimus 0.02% ointment is safe and effective in refractory ocular surface inflammation in pediatric patients. To the best of our knowledge, our study is the largest study to evaluate the safety of topical tacrolimus in pediatric patients with longest follow-up duration to date.

Abbreviations

AKC: Atopic keratoconjunctivitis; GVHD: Graft-versus-host disease; OCP: Ocular cicatricial pemphigoid; PKC: Phlyctenular keratoconjunctivitis; SIG: Steroid-induced glaucoma; SJS: Stevens–Johnson syndrome; VKC: Vernal keratoconjunctivitis.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of Yonsei University, Seoul, Republic of Korea (IRB number: 4-2019-1315), and the tenets of the Declaration of Helsinki were followed. Considering the retrospective nature of the study and the use of deidentified patient data, the written informed consent was waived by the Institutional Review Board of Yonsei University, Seoul, Republic of Korea.

Consent for publication

Not applicable (no identifying patient data).

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to protection of the patient's personal information but are available from the corresponding author on reasonable request.

Competing interests

The authors declare they have no competing interest.

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None.

Authors' contributions

KK, IJ acquired and analyzed the data, drafted the initial manuscript, and revised the manuscript. KYS, EKK, IJ conceptualized and designed the study, and collected data. TIK, KK, KYS conceptualized and designed the study, coordinated, and supervised data collection, analyzed the data, critically reviewed the manuscript, and revised the manuscript. All authors read and approved the final manuscript.

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None of the authors has a financial or proprietary interest in any material or method mentioned.

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Figures

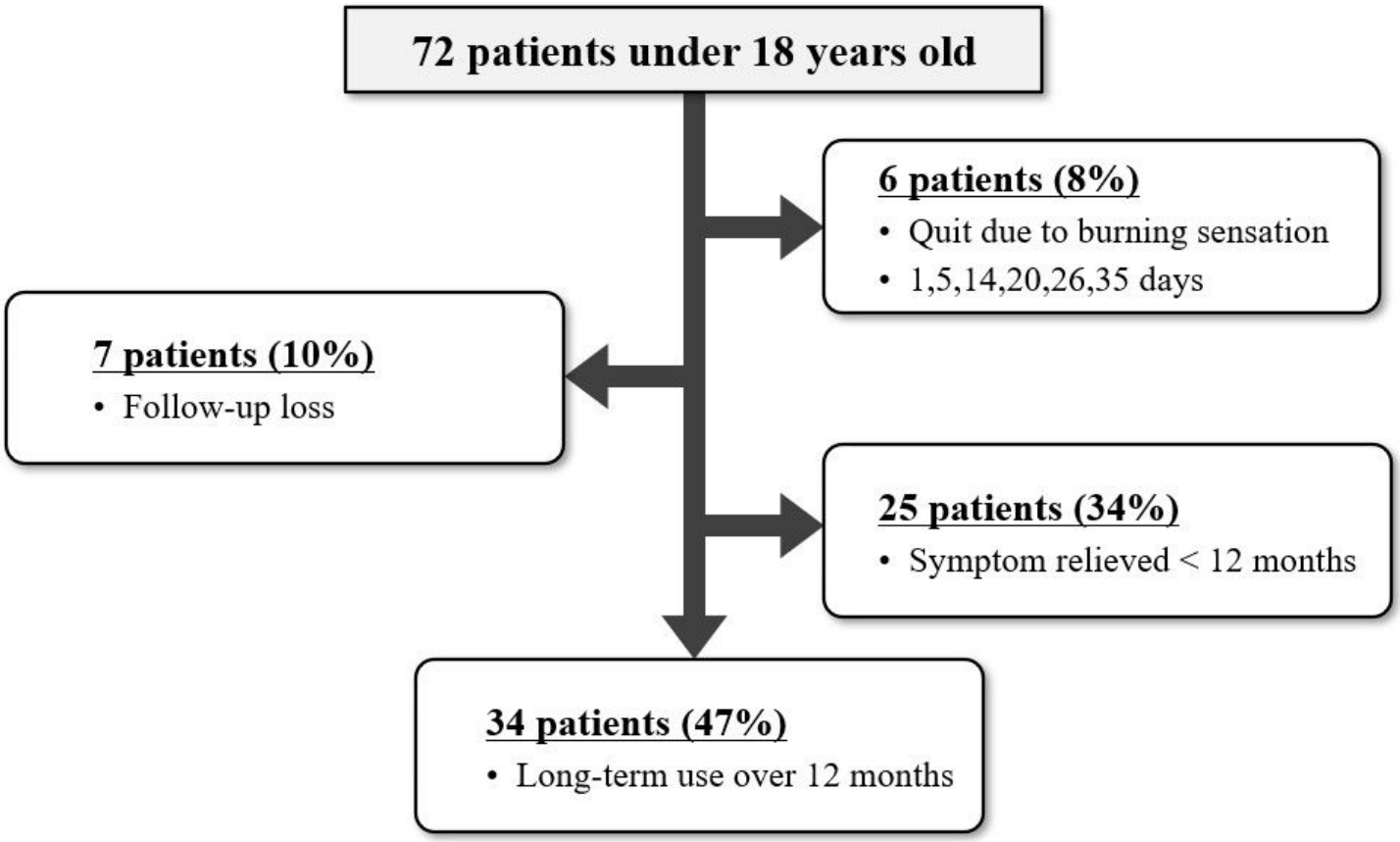

Figure 1

The flowchart of pediatric patients who were treated with the topical 0.02% tacrolimus ointment for ocular surface inflammation refractory to conventional therapy.

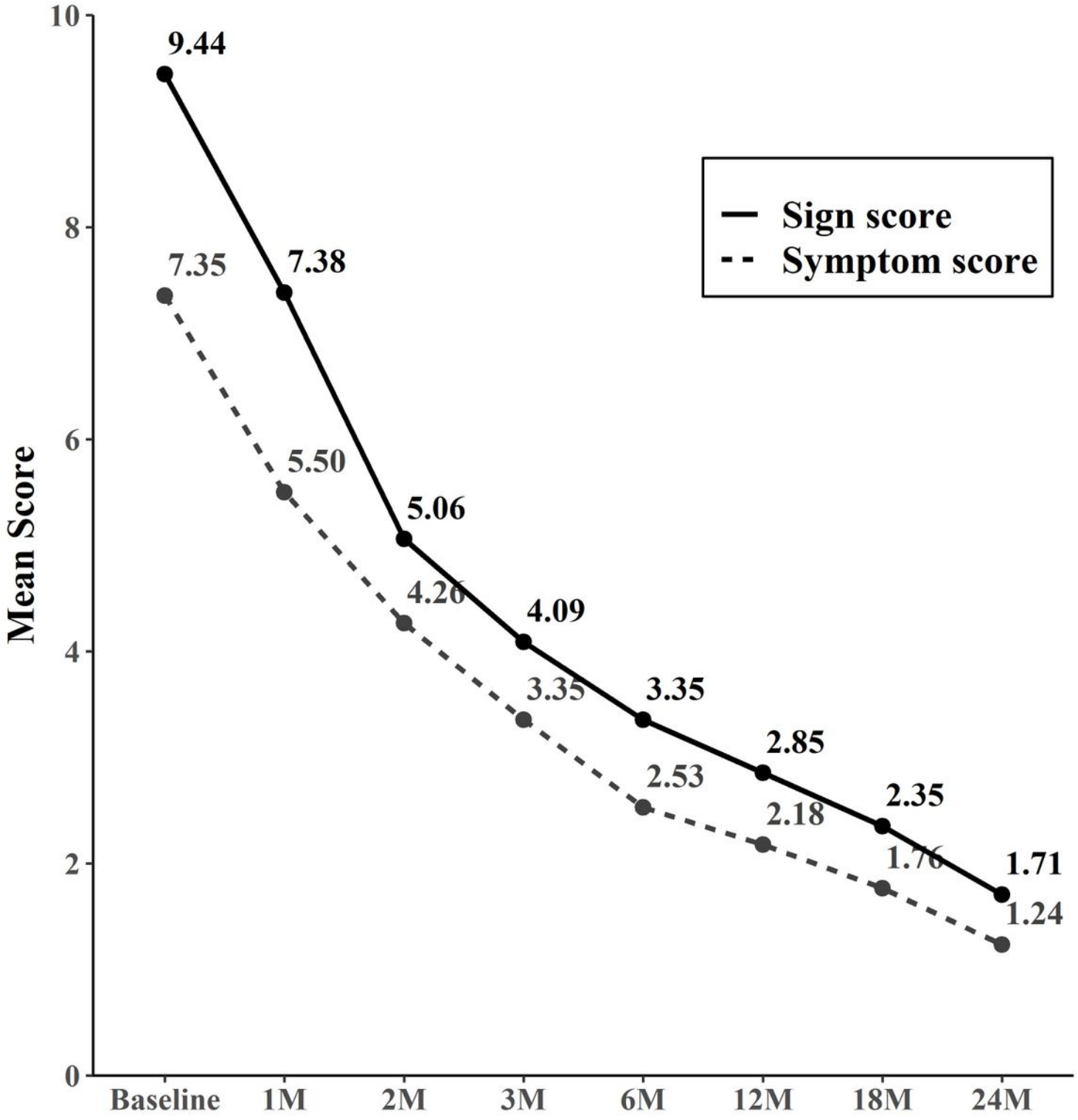

Figure 2

Comparison of overall symptom and sign score during the follow-up period. Both scores decrease during the treatment period.

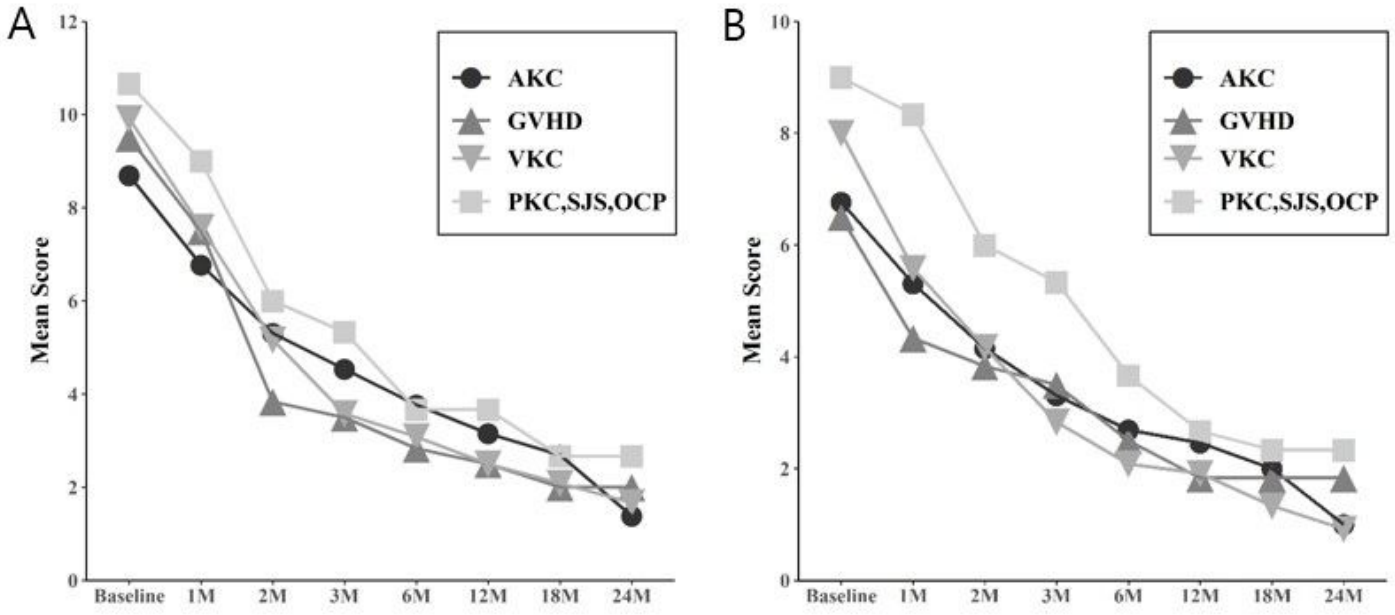

Figure 3

Comparison of each sign scores (a) and symptom scores (b) among disease groups during the follow-up period. It shows the changes in both scores during the treatment period for each disease.

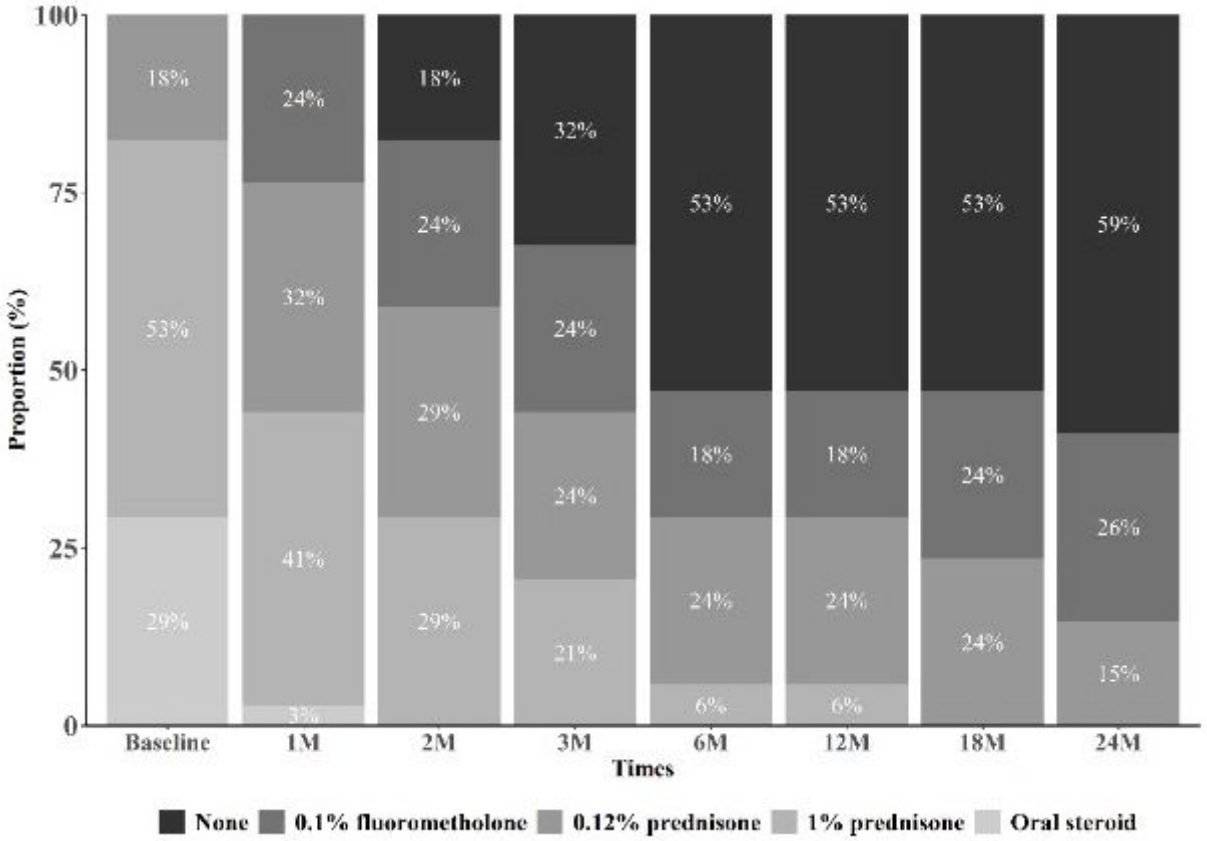

Figure 4

Changes in steroid use in combination with the tacrolimus ointment. It shows that the proportion and need of steroids decreases during the treatment period.