ORIGINAL RESEARCH

Predictive Factors of Suboptimal Response to Topical 0.1% Cyclosporine A Cationic Emulsion in Pediatric Vernal Keratoconjunctivitis: A Real-World Retrospective Study

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ABSTRACT

Introduction: Vernal keratoconjunctivitis (VKC) is a chronic, recurrent ocular surface disease of childhood that often requires long-term anti-inflammatory therapy beyond topical corticosteroids. This study aimed to identify the clinical predictors of suboptimal treatment response with 0.1% cyclosporine A cationic emulsion (CsA CE) in a real-world pediatric cohort.

Methods: This was a retrospective, single-center study including patients aged 4–18 years with moderate or severe VKC, evaluated at a multidisciplinary ophthalmology clinic between January 2021 and December 2024. All patients received 0.1% CsA CE (administered four times daily). Demographic, clinical, and anamnestic data were collected. Disease severity was assessed using the Bonini grading scale, which provides a semiquantitative evaluation of ocular signs and symptoms. Statistical analysis was performed using univariate and multivariate Cox regression. For significant parameters, ROC curves were generated and optimal cut-off values were identified using the Youden's Index.

Results: A total of 101 patients were included (mean age 8.86±3.31 years; 27 females). Over a mean follow-up period of 1.44±1.13 years, 18 patients (17.8%) required escalation to 1% CsA galenic eye drops, of whom seven were further switched to 0.1% tacrolimus galenic eye drops. On multivariate analysis, the baseline composite clinical score was the strongest predictor of suboptimal treatment response. Notably, the clinical signs score alone demonstrated superior discriminative ability (AUC 0.732) compared to the total score (AUC 0.714). Optimal cut-off values were identified as 7 for clinical signs and 15 for the overall score.

Conclusions: Baseline disease severity, particularly the score for clinical signs, is a reliable predictor of response to 0.1% CsA CE. In patients exceeding the identified thresholds, early therapeutic escalation may be warranted to improve disease control and prevent structural complications.

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Key Summary Points

Vernal keratoconjunctivitis (VKC) is a chronic ocular allergic disease affecting children, often requiring immunomodulatory therapy beyond antihistamines and corticosteroids.

Although 0.1% cationic cyclosporine A (CsA CE) is approved for severe VKC, early markers of suboptimal treatment response remain poorly characterized.

This study aimed to identify clinical predictors of suboptimal response to CsA CE in a real-world pediatric VKC cohort.

Higher baseline clinical sign scores were significantly associated with an increased risk of therapeutic failure, with receiver operating characteristic (ROC) curve analysis identifying optimal cut-offs (≥ 15 total score; ≥ 7 sign score).

Early identification of patients unlikely to respond to CsA CE may support timely therapeutic escalation and individualized treatment planning in VKC.

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, and often asymmetrical allergic inflammatory disorder affecting the anterior ocular surface [1]. This severe and frequently relapsing condition predominantly affects the pediatric population, typically exhibiting seasonal exacerbations during spring and summer months [1]. While topical corticosteroids are highly effective in controlling the acute signs and symptoms of VKC, their use is limited by potential dramatic adverse effects and the inability to use them for long-term applications [2–5]. Consequently, calcineurin inhibitors, such as cyclosporine and tacrolimus, have become indispensable alternatives for chronic management [3]. Historically, calcineurin inhibitors were utilized in local galenic (compounded) formulations [2]. A significant advancement occurred in 2020 with the licensing of cyclosporine A 0.1% cationic emulsion (CsA CE, Verkazia®) as the sole cyclosporine-based drug specifically approved for VKC [6]. This formulation, containing cyclosporine at a concentration approximately ten times lower than the standard galenic preparation (1%), was anticipated to demonstrate comparable efficacy due to its cationic emulsion matrix facilitating improved distribution on the ocular surface [6].

In recent years, this 0.1% CsA CE has indeed emerged as a first-line topical anti-inflammatory treatment, particularly for cases refractory to conventional therapy. However, despite its advantages, real-world experience suggests that a considerable proportion of patients still require treatment escalation, often necessitating higher concentrations of cyclosporine (e.g., 1% galenic eye drops formulations) or a switch to topical tacrolimus eye drops [2, 7]. This observation highlights a potential gap between the expected efficacy of the new licensed formulation and the persistent disease activity in some patients. This study aimed to identify potential clinical predictors of suboptimal treatment response with 0.1% CsA CE, defined as the need for therapeutic switch to either higher cyclosporine concentrations or tacrolimus, in a real-world pediatric cohort with VKC. By investigating factors associated with such treatment escalation, we seek to better define the indications for its prescription and optimize treatment strategies for patients affected by this challenging ocular disorder.

METHODS

This was a single-center retrospective study conducted at the Ophthalmology Unit of the IRCCS Ca' Granda Foundation Ospedale Maggiore Policlinico in Milan. It included pediatric patients aged between 4 and 18 years who were referred to the VKC-dedicated outpatient clinic between January 1, 2021, and December 31, 2024, with a clinical diagnosis of moderate to severe VKC. The study received approval from the local Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki. Owing to its retrospective nature and the use of anonymized data, the requirement for

written informed consent was waived, in compliance with current data protection regulations (EU Regulation 2016/679 – GDPR).

Eligibility and Treatment

Patients were eligible if they were between 4 and 18 years old, had a confirmed clinical diagnosis of moderate to severe VKC [8], and had been regularly followed at the dedicated outpatient clinic during the study period. All included patients had shown an inadequate response to first-line therapies, including topical antihistamines or mast cell stabilizers and short cycles of topical corticosteroids (pulse therapy), and were therefore switched to treatment with 0.1% CsA CE eye drops. Patients were excluded if they had a known hypersensitivity to cyclosporine A, evidence of ocular inflammation unrelated to VKC, systemic comorbidities, or concurrent treatments that could potentially interfere with the study outcomes. All patients received 0.1% CsA CE eye drops, which were typically administered four times daily at intervals of 6–8 h.

Clinical Assessment and Follow-up

Clinical data were retrospectively extracted from medical records starting from the baseline visit. The collected variables included demographic information such as sex and date of birth, and residential address, results of skin prick testing and personal history of atopic dermatitis—both obtained during the visit at the Pediatric Allergy Clinic of the Pediatrics and Pneumoinfectology Department, IRCCS Ca' Granda Foundation Ospedale Maggiore Policlinico in Milan—as well as the date of VKC diagnosis and the date of initiation of cyclosporine A 0.1% therapy. Subjective symptoms and objective clinical signs were documented using the Bonini grading scale [8]. Symptoms—including ocular itching, photophobia, foreign body sensation, mucous discharge, and tearing—were assessed individually in each eye and graded from 0 (absent) to 3 (severe). Clinical signs, evaluated by slit-lamp examination, included conjunctival hyperemia,

tarsal papillae, mucous discharge, Trantas dots, superficial punctate keratitis, shield ulcer, limbal neovascularization, and conjunctival scarring, each graded on the same 0 to 3 scale. All clinical evaluations recorded in the medical charts had been performed jointly by two ophthalmologists (S.O. and G.L.) with several years of experience in the management of vernal keratoconjunctivitis. Follow-up information was also retrieved from subsequent medical records and included the date of any therapeutic switch to a higher concentration of cyclosporine A (1% compounded formulation) or to topical tacrolimus 0.1% (compounded formulation), as well as the date of the last recorded visit at the VKC-dedicated outpatient clinic. According to the internal management protocol for VKC, a suboptimal response to 0.1% CsA CE therapy was defined as the requirement for at least two cycles of topical corticosteroids (rescue therapy) and/or a documented clinical deterioration in clinical scores at any point during the treatment period.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics software, version 29.0.2.0. The association between baseline clinical and demographic factors and the risk of suboptimal treatment response with 0.1% CsA CE was assessed using Cox proportional hazards regression analysis. An initial univariate analysis was conducted, followed by a multivariate model including only those variables that were statistically significant ($p < 0.05$) or showed a trend toward significance ($p < 0.1$) in the univariate analysis. For continuous variables identified as significant predictors of suboptimal treatment response, receiver operating characteristic (ROC) curves were generated to determine optimal cut-off values based on Youden's Index.

All statistical analyses were conducted using data from a single eye per patient. Specifically, the eye with the highest combined severity score for signs and symptoms at baseline was selected for analysis. In cases where both eyes

presented with identical scores, the right eye was chosen as the reference eye.

RESULTS

A total of 101 patients (27 females; mean age 8.86±3.31 years) who initiated therapy with 0.1% CsA CE were enrolled. The mean disease duration (from diagnosis to baseline visit) was 1.2±1.86 years. Among the included patients, 45 (44.55%) had atopic dermatitis, and 57 (56.43%) had a positive prick test. The mean follow-up duration was 1.44±1.13 years.

At the baseline visit, all patients were on topical ketotifen and had undergone an average of two cycles of topical dexamethasone in the previous month. The mean sum of symptom scores was 6.63±4.15 points, and the mean sum of sign scores was 7.24±2.89 points. The mean total clinical score (sum of symptom and sign scores) was 13.87±5.68 points.

During follow-up, 18 patients (17.8%) were switched to 1% cyclosporine galenic eye drops due to lack of disease regression, after a mean interval of 0.91±0.82 years from the baseline visit. Of these, seven were further switched to tacrolimus galenic eye drops due to persistent lack of clinical response, on average 0.69±0.7 years from baseline.

Table 1 presents the results of the regression analysis. In the univariate analysis, the total score, symptom score, sign score, and disease duration were significantly associated with therapeutic suboptimal response (Table 1). Given the correlation between the scores, two distinct multivariate models were conducted: one including only the total score, and the other with symptom and sign scores separately (Table 1).

In the first model, only the total score remained significantly associated with suboptimal therapeutic response (β coefficient: 1.123 [95% confidence interval: 1.047–1.206], $p = 0.001$). This suggests that the effect of disease duration might be partly explained by the overall severity of the clinical condition, which is better captured by the total score (sum of symptoms and signs). Although the two variables are not linearly correlated, they may share

Table 1 Results of Cox regression

Variable	Univariate analysis			Multivariate analysis					
	P value	Exp(B)	95.0% CI	*P* value	Exp(B)	95.0% CI	*P* value	Exp(B)	95.0% CI
Sex	0.054	0.400	0.157–1.017	0.216	0.526	0.190–1.456	0.169	0.489	0.176–1.355
Age	0.175	0.889	0.749–1.054	–	–	–	–	–	–
Disease duration	**0.033**	**0.614**	**0.392–0.962**	0.066	0.613	0.364–1.034	0.077	0.629	0.376–1.051
Cortisone cycles	0.287	0.876	–	–	–	–	–	–	–
Total score	**<.001**	**1.159**	**1.078–1.246**	**0.001**	**1.123**	**1.047–1.206**	–	–	–
Symptom score	**0.002**	**1.128**	**1.047–1.215**	–	–	–	0.076	1.094	0.991–1.208
Sign score	**0.003**	**1.315**	**1.098–1.575**	–	–	–	**0.008**	**1.269**	**1.064–1.514**
Positive prick test	0.183	2.792	0.616–12.662	–	–	–	–	–	–
Presence of atopic dermatitis	0.848	1.095	0.432–2.77	–	–	–	–	–	–

Significant variables are highlighted in bold

a common component in determining the outcome, making the total score a more informative predictor. The addition of an interaction term between overall clinical score and disease duration did not reach statistical significance ($p = 0.902$), suggesting that the predictive effect of the clinical score does not depend on disease duration. In the second model (Table 1), only the sign score was confirmed to be significantly associated with the outcome (β coefficient: 1.269 [95% confidence interval: 1.064–1.514], $p = 0.008$). Although the two components (symptom and sign scores) are weakly but significantly correlated ($r = 0.227$; $p = 0.006$), it is plausible that they share a portion of predictive information. In this context, the clinical sign score appears to be the most informative component in estimating the risk of suboptimal response.

Figure 1 illustrates the ROC curves constructed for both the overall clinical score and the clinical sign score in predicting suboptimal treatment response 0.1% CsA CE. The area under the curve (AUC) for the overall clinical score was 0.714, with an optimal cut-off value of 15 identified using Youden's Index. The AUC for the clinical sign score was slightly higher, at 0.732, with an optimal cut-off value of 7.

In the Cox regression analysis, an overall Bonini score ≥ 15 at baseline was significantly associated with an increased risk of suboptimal treatment response (hazard ratio = 4.785; 95% confidence interval: 1.546–14.808; $p = 0.007$). A clinical sign score ≥ 7 at baseline was significantly associated with an increased risk of suboptimal treatment response (hazard ratio = 4.617; 95% confidence interval: 1.316–16.200; $p = 0.017$).

Analyzing patients for whom tacrolimus therapy was prescribed, no significant differences were observed at baseline in either the overall clinical score (18 ± 8.04 points in patients treated with 1% cyclosporine versus 17.17 ± 4.71 points in patients subsequently switched to tacrolimus; $p = 0.961$, Mann–Whitney U test for independent samples) or, specifically, in the clinical sign score (8.81 ± 2.6 points for patients on 1% cyclosporine and 9.67 ± 2.6 points for those switched to tacrolimus; $p = 0.733$, Mann–Whitney U test for independent samples).
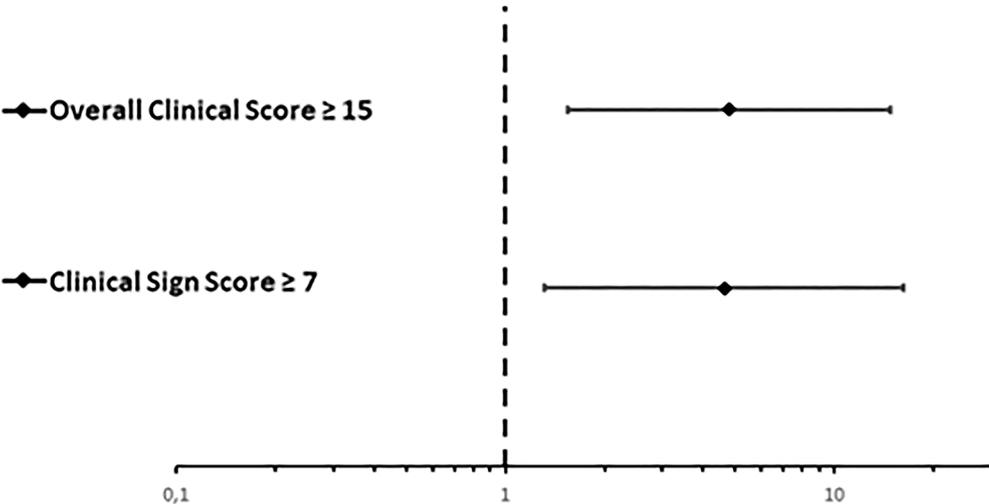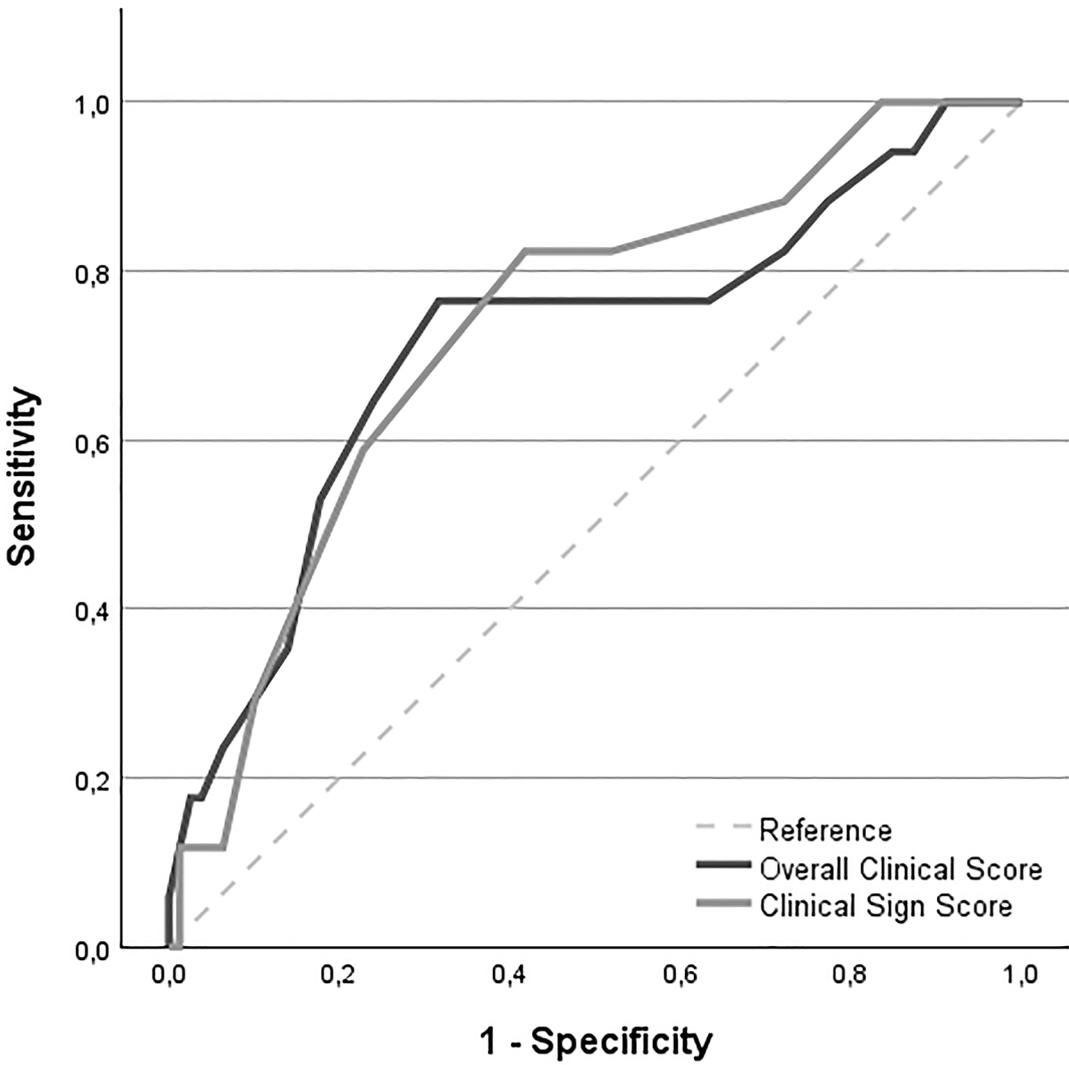
DISCUSSION

This study aimed to identify clinical predictors of suboptimal response to 0.1% cationic cyclosporine nanoemulsion (CsA CE) in pediatric patients with moderate or severe VKC, with the goal of optimizing therapeutic strategies based on baseline disease characteristics. Our results demonstrate that initial clinical severity, and in particular the objective clinical sign score, is the strongest predictor of treatment response. ROC analysis yielded clinically relevant thresholds (≥ 15 for the total score and ≥ 7 for the sign score), above which the likelihood of suboptimal response increased by more than fourfold. These findings provide a quantitative, evidence-based framework to guide early clinical decisions regarding therapeutic escalation.

Notably, while subjective symptoms such as itching and photophobia are often the primary reason for seeking medical care, our data indicate that objective signs—such as conjunctival hyperemia, tarsal papillae, and corneal involvement—are more reliable predictors of treatment trajectory. This aligns with the pathophysiological understanding of VKC as a disease driven by chronic eosinophilic inflammation, which may persist and progress even in the presence of partial symptomatic relief [1].

Notably, no significant differences in baseline scores were observed between patients who remained on 1% cyclosporine and those who were subsequently switched to tacrolimus. As described in our protocol, escalation was defined by the need for at least two rescue courses of topical corticosteroids and/or a documented worsening of clinical scores during treatment. Therefore, the decision to escalate to tacrolimus was primarily driven by the longitudinal disease course under 1% cyclosporine, rather than by baseline severity alone. In addition, the small number of patients escalated to tacrolimus ($n = 7$) reduced the statistical power to detect baseline differences.

Overall, our findings are consistent with those of a previous study conducted within our same institution, which documented early suboptimal response in approximately 16% of pediatric patients treated with CsA CE, with clinical

◄**Fig. 1** *Top* Combined ROC curves for the overall clinical score and the clinical sign score. *Bottom* Forest plot showing that an overall clinical score ≥ 15 or a clinical sign score ≥ 7 at baseline were significantly associated with an increased risk of suboptimal treatment response to cyclosporin 0.1%

improvement following therapeutic intensification [7]. Our study builds upon this evidence by providing objective, quantitative thresholds to support clinical decision-making and by applying a validated severity scale in a larger real-world cohort. The favorable tolerability and anti-inflammatory efficacy of the cationic nanoemulsion, previously reported, were confirmed in our population, particularly among patients with lower baseline severity.

Our findings are also aligned with those of Caputo et al., who demonstrated a rapid and significant reduction in conjunctival hyperemia and limbal papillae already after 1 month of treatment with CsA CE in a pediatric cohort with moderate VKC, without the need for additional steroid therapy [9]. Similarly, Salami et al. reported significant improvement in both signs and symptoms of severe VKC in patients treated with CsA CE, coupled with high subjective satisfaction scores [10]. However, in that study, more than half of the patients required short rescue courses of topical dexamethasone during follow-up. Compared to these reports, our study provides novel evidence by identifying baseline clinical thresholds predictive of suboptimal treatment response, and by documenting a structured escalation path from CsA CE to higher-concentration galenic formulations or tacrolimus in nearly 18% of patients. The absence of predictive analyses or switch data in the aforementioned studies underlines the added value of our work in supporting early personalized treatment planning.

Although the presence of atopic dermatitis was included in our analysis, it was not significantly associated with suboptimal response to treatment. This contrasts with the findings of Shimokawa et al., who identified atopic dermatitis and male sex as predictors of poor long-term disease control in a Japanese cohort managed with proactive tacrolimus [11]. The differing

results may reflect variations in study design, follow-up duration, outcome definitions, and therapeutic strategies. While Shimokawa et al. focused on long-term remission, our study addressed early response dynamics under real-world conditions with CsA CE. It is conceivable that atopic dermatitis plays a more prominent role in disease chronicity rather than in short-term therapeutic efficacy.

The weak association between disease duration and response suggests that CsA CE is more effective in early-stage disease, when inflammation is predominantly functional and still reversible. In more advanced cases, irreversible structural alterations such as shield ulcers, epithelial remodeling, and conjunctival fibrosis may reduce drug responsiveness despite good adherence [1]. This underlines the need for early identification of patients at higher risk of suboptimal response, in order to optimize therapeutic strategies and prevent progression. Despite its lower concentration compared to traditional galenic formulations, CsA CE benefits from enhanced ocular surface retention and bioavailability due to its cationic emulsion [12–14]. However, our findings indicate that this advantage may not be sufficient in patients with high-grade baseline inflammation. To our knowledge, this is the first study to define quantitative, clinically validated thresholds for predicting suboptimal response to CsA CE in VKC, providing a practical framework for early risk stratification and treatment planning.

Strengths of this study include its relatively large sample size, the use of a standardized and validated clinical grading system, and the application of ROC-based threshold analysis. Limitations include the retrospective design and the absence of biomarker or imaging-based data, which may further improve predictive models.

Conclusions

In conclusion, CsA CE is a safe and effective first-line treatment for pediatric VKC, particularly in patients with mild to moderate baseline severity. The clinical sign score at treatment initiation is the most reliable predictor of suboptimal response. The identification of objective cut-off

values supports early recognition of patients who may benefit from therapeutic intensification. These findings contribute to the development of more individualized and evidence-based management strategies for VKC and warrant confirmation through prospective, multicenter studies.

Declarations

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