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BRIEF REPORT

# Clinical Outcomes of Topical 0.1% Ciclosporin Cationic Emulsion Used on Label in Children with Vernal Keratoconjunctivitis

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## ABSTRACT

***Introduction***: The purpose of this short article is to report the clinical outcomes of topical 0.1% ciclosporin cationic emulsion (CsA-CE) used on label in children with vernal keratoconjunctivitis (VKC).

***Methods***: In this prospective, non-comparative, observational study children affected by active severe VKC were treated for at least 12 months with topical 0.1% CsA-CE. The drug was instilled in both eyes 4 times daily. Data collected from medical charts for the baseline visit (T0) and 1-year follow-up visit (T1) included symptomatic score (0–15), clinical score (0–15), side effects, rescue therapy (need and total number of courses with 0.1% dexamethasone 4 times daily for 5 days), ocular complications and tolerability (visual analog scale [0–100]).

***Results***: Data from 25 children (20 boys, 5 girls; mean [± standard deviation] age 8.40 ± 2.54 years) were included in the study. Of the 25 patients, 23 (92%) used 0.1% CsA-CE eye drops as per label recommendations, including four patients who had prematurely stopped using topical galenic CsA due to side effects. Symptomatic and clinical scores decreased significantly after treatment, with the mean symptomatic score decreasing from 9.76 ± 1.27 at T0 to 3.80 ± 1.08 at T1, and the mean clinical score decreasing from 9.20 ± 1.32 at T0 to 3.44 ± 1.00 at T1; both $P < 0.0001$). Five patients (20%) required at least one course of rescue medication (mean 3.4 ± 4.8 courses/year). No patients experienced ocular complications during the study, and treatment tolerability was very high (mean score 89.40 ± 5.46).

***Conclusion***: Our findings confirm that topical CsA-CE is an effective on-label option for children with VKC in the real-life setting. In our pediatric patient population, CsA-CE provided good clinical outcomes with a limited need for rescue medication, and it was well tolerated by almost all patients, including those who were intolerant to galenic formulations.

**Keywords:** Allergic keratoconjunctivitis; Cationic emulsion; Ciclosporin; Verkazia; Vernal keratoconjunctivitis

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**Key Summary Points**

*Why carry out this study?*

Alternative therapies for the treatment of vernal keratoconjuctivitis (VKC) will greatly reduce the risks of corticosteroid-induced glaucoma and cataract.

Nanotechnologies can be exploited to improve ocular delivery of ophthalmic drugs, especially in the pediatric patient population children for whom treatment adherence may be problematic.

Understanding the tolerability and the bioavailability of the new drug formulation of topical 0.1% ciclosporin cationic emulsion (CsA-CE) compared to galenic formulations may guide the treatment choices in medical practice.

*What was learned from the study?*

Patients with patients were well controlled with 0.1% CsA-CE eye drops without the need for chronic topical corticosteroids.

The drug was well tolerated in almost all treated patients, including those who had previously shown intolerance to ciclosporin galenic formulations.

## INTRODUCTION

The external eye and its adnexa are designed to protect the internal ocular structures, in particular from harmful chemicals, thanks to the presence of various barriers. The eyelids act as a shutter preventing foreign substances from coming into contact with the ocular surface; tears are continuously secreted to wash exogenous substances off the ocular surface; and the cornea forms a tight structural barrier made of three different tissue layers with alternating hydrophilic and lipophilic properties to prevent the intraocular absorption of unwanted substances [1].

Nanotechnologies/nanoformulations are currently considered to be the best strategies to improve the ocular delivery of ophthalmic drugs. The Novasorb® technology platform developed by Novagali Pharma S.A. (Évry-Courcouronnes, France) is based on the cationic nanoemulsion approach and exploits the negative charge expressed by corneal and conjunctival cells and the mucus layer of glycosyl amino glycans lining the ocular surface [1–3]. The application of a positively charged formulation to the eye results in an electrostatic attraction that prolongs the residence time of the formulation on the ocular surface. In addition, the nanosize of the oil droplets creates a large contact surface with the ocular surface cells, enabling enhanced absorption [4].

Verkazia® (Santen Pharmaceutical Co., Ltd., Japan) is a new eye drop formulation consisting of 0.1% (1 mg/mL) ciclosporin (CsA) in cationic emulsion (CE) based on the Novasorb technology. It is the first topical CsA formulation to be licensed in Europe, Canada and Asia for the treatment of severe vernal keratoconjunctivis (VKC) in children aged 4 to 18 years; in the USA, the formulation has also been approved, but without any limitation of disease severity and patient age [5]. VKC is a rare, bilateral, chronic allergic disease affecting the conjunctiva and the cornea of school-age children. Symptoms include intense ocular itching, foreign body sensation, tearing, mucous discharge and photophobia. Signs include conjunctival hyperemia, tarsal papillary hyperplasia, gelatinous limbal infiltrates with chalky white nodules (Horner-Trantas dots), superficial punctate keratitis and, in more severe cases, corneal shield ulcers. VKC may present as a purely palpebral phenotype or with purely limbal involvement, or as both (mixed forms). It often presents seasonally, but in more severe cases it may have a chronic, exacerbating course [6–8].

The pathophysiology of the underlying immunologic reaction remains as yet unresolved. Recent evidence supports the presence of an immunoglobulin E-dependent hypersensitivity reaction, with mast cell degranulation and subsequent release of several mediators that lead to vasodilatation, edema, hyperemia and the recruitment of other inflammatory cells.

These induce fibroblast activation and conjunctival tissue remodeling with collagen deposition and giant papillae formation. Other studies have highlighted a possible role for CD4 T helper 2 (Th2)-driven type IV (delayed or cell-mediated) hypersensitivity reaction in the pathophysiology of VKC [8–10].

The conventional treatment for VKC is based on physical removal of conjunctival debris from the conjunctival surface by eye rinsing and compression with a cool, soothing saline solution or artificial tears. First-line topical therapy includes ophthalmic preparations of antihistamines (e.g. levocabastine and epinastine), mast cell stabilizers (e.g. sodium cromoglycate, ketotifen and lodoxomide) and dual-acting agents (e.g. olopatadine). Such treatments are usually sufficient to induce remission in mild forms of the disease, while severe disease forms may require the chronic or recurrent use of topical corticosteroids. Immunomodulatory agents, including tacrolimus and CsA, can suppress inflammation while avoiding/reducing the use of corticosteroids. CsA is a calcineurin inhibitor that acts on T cell activation. In particular, it inhibits the activation of the nuclear factor of activated T cells (NF-AT), a transcription factor that promotes the synthesis of pro-inflammatory factors. Interleukin-2 is especially necessary for T cell activation and proliferation and is believed to be responsible for CsA's immunosuppressive actions [11]. CsA is a lipophilic substance and was formerly instilled topically using hydrophobic solutions, but these formulations were characterized by poor drug bioavailability and low patient tolerability [10]. In fact, such compounds are generally prepared by pharmacists (galenic formulations) from injectable preparations and contain ethanol as co-solvent. To cope with this issue, CsA-in cationic emulsion (CE) 0.1% has been developed and found to have an acceptable safety profile [12]. Subsequently, the efficacy and safety of CsA-CE for treating children with VKC have been reported in VEKTIS studies [7, 13].

The aim of this study was to describe the real-life experience of two Italian centers in the management of VKC with on-label 0.1% CsA-CE and to report the 1-year safety and efficacy outcomes.

## METHODS

This prospective non-comparative observational study was conducted in two Italian centers (University Magna Graecia of Catanzaro and IRCCS Ospedale Policlinico San Martino, University of Genoa). The study protocol was approved by the local Ethics Committee (Comitato Etico Regione Calabria–Sezione Area Centro Protocol code: 82-2022; Approval date: 19 May 2022). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Before any procedure was initiated, parents signed a written informed consent form after receiving an explanation of the study protocol.

Consecutive children aged 4 to 18 years with active severe VKC (grades 3–4 on the Bonini scale) [14] were enrolled into the study and followed up for a minimum period of 12 months. Exclusion criteria were ocular surface diseases other than VKC, altered lid anatomy or function, abnormal nasolacrimal drainage, any other ocular condition requiring concomitant topical treatments, systemic corticosteroid use, previous or active systemic allergies, hypersensitivity to the active substance or to any of the excipients, ocular or peri-ocular malignancies or premalignant conditions and/or active or suspected ocular or peri-ocular infection. The clinical form of the disease was classified according to phenotype (limbal,

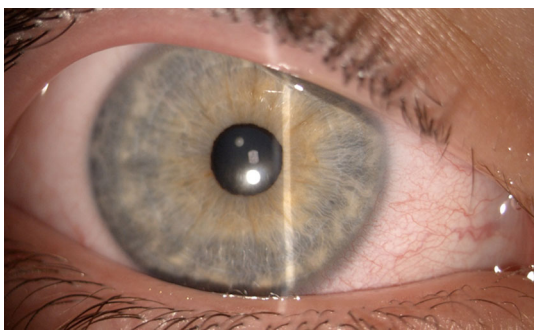

**Fig. 1** Bulbar conjunctival hyperemia in a patient affected by vernal keratoconjuctivitis (VKC)

palpebral or mixed). Patients were prescribed 1 drop of CsA-CE (1 mg/mL) 4 times daily. If symptom control was not obtained and/or Bonini scale's grade worsened despite CsA-CE treatment, a course of rescue medication (0.1% dexamethasone 4 times daily for 5 days) was added to the treatment regimen. Data were collected from medical charts for the baseline visit (T0) and the 1-year follow up visit (T1), including symptomatic score (scale of 0–15, covering itching, discomfort, tearing, discharge, photophobia) [13], clinical score (scale of 0–15, covering hyperemia, tarsal papillae, Horner-Trantas dots, keratopathy, neovascularization) (Figs. 1, 2, 3) [15], side effects, rescue therapy (need and total number of courses), ocular complications and tolerability (visual analog scale (ranging from 0 [none/not at all] to 100 [much/very]).

Statistical analysis was performed using GraphPad Prism 8.2.1 (GraphPad Software, Inc., San Diego, CA, USA). Descriptive statistics were computed for all variables. Paired *t*-test was used to compare scores before and after treatment. A $P$ value $< 0.05$ was considered to indicate statistical significance.

## RESULTS

Overall, data from 25 children (20 boys, 5 girls; mean [± standard deviation] age 8.40 ± 2.54 years, age range 4–17 years) were included in the study analysis. Of the 25 patients, five (20%) were affected by limbal VKC, 11 (44%) had purely palpebral forms and nine (36%) had a mixed phenotype. Five patients (20%) had previously been treated with galenic formulations of CsA, of whom four had stopped use due to an intense burning sensation and red eye upon instillation. Almost all patients (23/25, 92%) used CsA-CE 0.1% eye drops as per recommendations, including those patients who had prematurely interrupted the use of topical galenic CsA due to side effects; the remaining two patients (8%) (both CsA-naïve) prematurely stopped the study treatment after 2 months due to a burning sensation upon drug instillation.

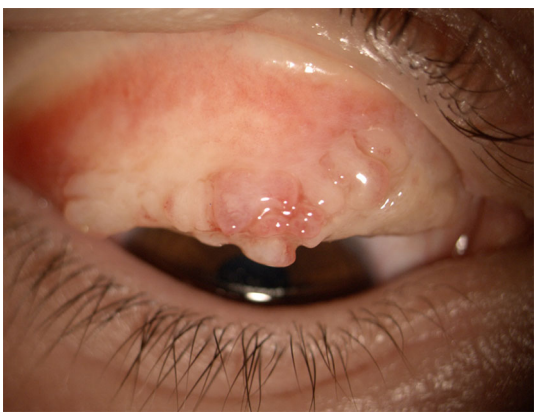

**Fig. 2** Giant papillae on the upper tarsal conjunctiva in a patient affected by VKC

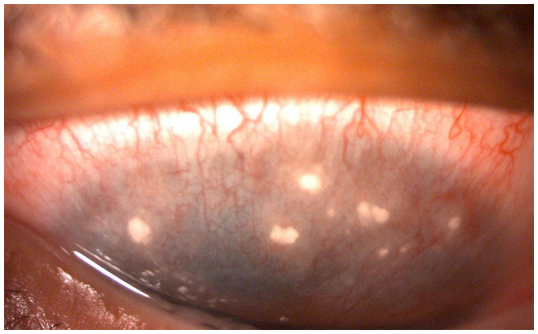

**Fig. 3** Horner-Trantas dots and corneal neovascularization in a patient affected by VKC

Symptomatic and clinical scores decreased significantly after treatment, with the mean (± SD) symptomatic score decreasing from 9.76 ± 1.27 at T0 to 3.80 ± 1.08 at T1 ($P < 0.0001$), and the mean clinical score decreasing from 9.20 ± 1.32 at T0 to 3.44 ± 1.00 at T1 ($P < 0.0001$).

Five patients (20%) required at least one course of rescue medication (mean of 3.4 ± 4.8 courses/year, range 1–12 courses/year). No patients experienced ocular complications throughout the entire study. At T1, treatment tolerability was very high (mean score 89.40 ± 5.46, range 80–100).

## DISCUSSION

In the present observational non-controlled study, on-label treatment with the new CsA-CE 0.1% eye drop formulation provided a

significant improvement of both clinical and symptomatic scores in children with severe active VKC. A large majority (80%) of patients were able to control their disease without the need for topical corticosteroids; in addition, the latter were used only sporadically in all of the remaining cases except one. Almost all patients in the study followed the treatment according to the prescribed posology, and a very high tolerability profile was reported by all of them, including those who had prematurely discontinued galenic CsA formulations due to side effects.

The main findings of this study are consistent with those reported in previous studies on the use of CsA for VKC [7, 13]. In particular, the VEKTIS study showed that pediatric patients treated with CsA-CE eye drops achieved significant improvements in both the signs and symptoms of severe VKC compared to patients who received vehicle alone, with the study group receiving the high-dose CsA-CE 0.1% formulation showing more numerous conclusive statistical results versus vehicle than the low-dose study group, much larger improvements in photophobia and mucous discharge and much larger improvements for quality of life [7].

Following the recent authorization of CsA-CE 0.1% for on-label use in the setting of VKC, a few studies have reported the real-world outcomes of this treatment [15–17]. Salami and collaborators reported the first subjective satisfaction data, based on a cohort of patients who used the on-label CsA-CE 0.1%; the authors reported significant reduction of signs and symptoms and an overall subjective satisfaction with a good compliance, limited use of corticosteroids and no logistic problems experienced by patients or caregivers [16]. The second study compared safety and efficacy outcomes of CsA-CE 0.1% with a hospital preparation of 2% CsA obtained by the dilution of an intravenous preparation 50 mg/mL CsA in macrogolglycerol ricinoleate [15]. Both treatments (CsA-CE 0.1% and 2% CsA) led to a favorable evolution in clinical and symptomatic scores and reduced corticosteroid use, with a similar tolerability profile. However, it should be pointed out that patients randomized to the 0.1% CsA-CE arm were able to control their signs and symptoms by varying (lowering) the number of daily instillations of the drug. CsA-CE 0.1% can be considered an interesting alternative to the hospital preparation formulation, particularly due to its commercial availability and ease of handling. CsA is a lipophilic substance that is practically insoluble in water; therefore, it must be delivered topically to the eye in a lipid-based system. The CsA-CE formulation is a cationic emulsion that is attracted to the negatively charged particles of cell membranes, thereby increasing its retention on the ocular surface [18] and explaining the similar efficacy to 2% CsA despite a dose that is 20-fold lower [19].

The treatment of VKC is troublesome due to the demographic characteristics of the young patients and the chronicity of the disease, particularly in the severe forms. In this context, the use of a drug with a high tolerability profile is paramount, as it directly affects treatment adherence. Moreover, the significant reduction in the use of topical corticosteroids due to the availability of this therapy greatly reduces the risks of corticosteroid-induced glaucoma and cataract. The most important open issue that remains to be solved with this treatment is related to the posology that is not "student-friendly" since it is known that it can be challenging to instill four drops per day during the school period. Moreover, the long-term effects of this agent are still to be defined, given the relatively short follow-ups described in literature.

The main limitation of the present study is the lack of a control group. However, it should be noted that the primary objective of this real-life study was focused on the initial clinical experience with the new on-label CsA-CE 0.1% formulation.

## CONCLUSIONS

Our findings suggest that in a real-life setting, CsA-CE 0.1% eye drops are well tolerated, as demonstrated in almost all of our patients, including those who had previously shown intolerance to CsA galenic formulations. This result supports the theory of a probable

superiority of CsA-CE 0.1% with respect to topical galenic CsA in terms of tolerability in this very young population. Furthermore, CsA-CE 0.1% eye drops allowed a better control of VKC signs and symptoms, eliminating the adverse effects associated with the use of both corticosteroids and CsA galenic formulations.

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***Disclosures.*** Giuseppe Giannaccare, Costanza Rossi, Massimiliano Borselli, Chiara Bonzano, Giovanna Carnovale Scalzo, Massimo Nicolò, Vincenzo Scorcia, Carlo Enrico Traverso and Aldo Vagge have nothing to disclose.

***Compliance with Ethics Guidelines.*** The study protocol was approved by the local Ethics Committee (Comitato Etico Regione Calabria–Sezione Area Centro Protocol code: 82-2022; Approval date: 19 May 2022). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Before any procedure was initiated, parents signed a written informed consent form after receiving an explanation of the study protocol.

***Data Availability.*** The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.



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