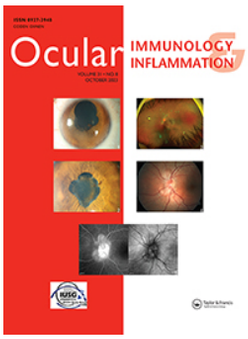

Ocular Immunology and Inflammation

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ioii20

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To cite this article: Marc Labetoulle, Andrea Leonardi, Pierre-Jean Pisella & Christophe Baudouin (2023) Ciclosporin A Cationic Emulsion 0.1% for the Management of Dry Eye Disease: Facts That Matter for Eye-Care Providers, Ocular Immunology and Inflammation, 31:8, 1707-1715, DOI: 10.1080/09273948.2022.2088566

To link to this article: https://doi.org/10.1080/09273948.2022.2088566

Published online: 29 Jun 2022.

OCULAR IMMUNOLOGY AND INFLAMMATION
2023, VOL. 31, NO. 8, 1707–1715
https://doi.org/10.1080/09273948.2022.2088566

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INVITED REVIEW

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Ciclosporin A Cationic Emulsion 0.1% for the Management of Dry Eye Disease: Facts That Matter for Eye-Care Providers

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ABSTRACT

Dry eye disease (DED) is a chronic inflammatory disease of the ocular surface requiring long-term therapy. Severe forms of DED generally do not respond to tear substitutes alone or combined, and often require treatment with topical anti-inflammatory agents to break the vicious circle of inflammation. This review summarises data from randomised controlled trials and real-world evidence on the efficacy and safety of ciclosporin A 0.1% cationic emulsion (Ikervis®) for the management of DED. Improvements in clinical signs and symptoms were reported from as early as 4 weeks after treatment initiation, although it can take a few months to reach the full benefits. Treatment periods of up to 12 months provide sustained benefit to patients. In the most responsive patients, treatment discontinuation is possible with no further substantial relapse over 12 months in over 65% of patients. Transient local ocular effects are the most commonly reported adverse events.

ARTICLE HISTORY
Received 24 March 2022
Revised 06 May 2022
Accepted 6 June 2022

KEYWORDS
Ciclosporin; corneal healing; dry eye disease; expert review; keratitis; literature review

Dry eye disease (DED) is a relatively common heterogeneous disease of the ocular surface, which has a noteworthy impact on an individual's quality of life due to visual impairment and discomfort.[1] Symptoms and clinical signs of DED can be improved by pharmacological and procedural treatments; nevertheless, chronic therapy and patient compliance are essential for effective achievement of good long-term outcomes.[1]

One such pharmacological treatment is topical ciclosporin A (CsA), which is currently available in a number of different formulations worldwide, including a 0.05% ophthalmic emulsion (Restasis®, Allergan), which was the first formulation approved in the USA and a 0.1% ophthalmic cationic emulsion (CE) (Ikervis®, Santen), which was the first approved formulation in Europe.[2,3] Although a number of studies have been conducted to evaluate the efficacy and safety of topical CsA for the management of DED, the global evidence to date is difficult to evaluate cohesively because studies vary significantly in design, inclusion criteria, length of follow-up and outcome measures evaluated.[4,5] Furthermore, there is limited literature available regarding the long-term follow-up of patients treated with topical CsA, optimal duration of treatment and identification of the group of individuals who may benefit the most from this treatment approach.[4]

Since the 2015 approval by the European Medicines Agency of CsA CE 0.1% for the management of severe keratitis in DED, there has been a need for an up-to-date and in-depth summary of available efficacy and safety data for this product, focussing on long-term data, correlation of clinical trials with real-world evidence (RWE) and optimal use in clinical practice for all eye-care providers. The aim of this article is to review the available published literature on the efficacy and safety of CsA CE 0.1% for DED, covering both clinical trial and RWE data.

Dry eye disease: a chronic disease requiring long-term treatment

DED has been defined by the Tear Film and Ocular Surface Society International Dry Eye Workshop (TFOS DEWS) II as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[6] In a more recent effort at achieving a global consensus, a group of DED experts proposed the following definition of DED: "Dry eye is a multifactorial disease characterized by a persistently unstable and/or deficient tear film causing discomfort and/or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation and neurosensory abnormalities."[7]

The key underlying pathophysiological mechanisms of DED are tear film instability, tear hyperosmolarity, apoptosis of cells on the ocular surface and inflammation; these aetiologies are connected to each other, forming the so-called vicious circle of DED and a self-perpetuating condition.[8–10] DED is therefore considered to be a chronic inflammatory disease known to be triggered by numerous extrinsic factors (e.g. desiccating

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environment, environmental exposure to irritants, digital device use, contact lenses, drying medications), intrinsic factors (e.g. ageing, autoimmunity, microbial stress) or a combination of any of these.[5,11,12] Although the disease can vary in severity and duration among patients, it typically exhibits fluctuations or gradual increases in the symptom severity.[1] The ongoing disease pathophysiology results in the need for long-term treatment, with a key goal of restoring homeostasis of the ocular surface and breaking the vicious circle.[5,11]

DED can be classified according to aetiology into one of two predominant types: aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE).[6] These diagnoses are not mutually exclusive and exist on a continuum; therefore, patients may have a mixed type DED, encompassing elements of both ADDE and EDE. As the disease progresses, it is more likely that characteristics of both forms will become apparent. ADDE encompasses conditions affecting the lacrimal gland, whereas EDE relates to conditions affecting the eyelid or ocular surface.

Typical signs and symptoms of DED include ocular irritation, discomfort, redness, mucous discharge, visual disturbances and plugged meibomian glands.[1] Ocular lubricants are the accepted first-line treatment of DED and remain the basis of management strategies aimed at reducing these signs and symptoms. However, they can be insufficient, even when combined, in cases of DED-related keratopathy and when there is a strong inflammatory component to the underlying pathophysiology. More advanced therapies are required for more severe forms of DED; such treatments include those that aim to reduce inflammation, for example topical corticosteroids, lifitegrast and topical CsA.[1,4,5] However, topical corticosteroids can only be used for short periods of time due to the risk of ocular hypertension, cataracts and opportunistic infections with prolonged use.[1,5] Lifitegrast is a small molecule integrin antagonist that is approved in the USA for treating signs and symptoms of DED, based on evidence from clinical trials.[5]

CsA has both immunomodulatory and anti-inflammatory properties, and in DED has been shown to reduce markers of inflammation, reduce tear hyperosmolarity, recover goblet cell density and have an anti-apoptotic effect.[5] The poor water solubility of CsA makes it challenging to formulate an effective and tolerable ocular drug-delivery system. More recently, marketed products have employed strategies, such as emulsions or nanomicelles, to overcome this issue, using CsA concentrations of 0.05% to 0.1%.[13] Ikervis® is formulated as a CsA 0.1% ophthalmic cationic oil-in-water emulsion. The cationic vehicle is thought to penetrate the negatively charged corneal and conjunctival cells more readily than anionic solutions, and therefore enhance the residence time of CsA on the ocular surface.[2,13] CsA CE 0.1% is used not only in the treatment of DED, but also in another ocular inflammatory condition, vernal keratoconjunctivitis (VKC).[14,15]

Effective DED management depends on patient education

Effective disease management requires education of patients on the chronic nature of the disease and its prognosis, and therefore the need for ongoing treatment.[1,5,13,16,17] Healthcare professionals should highlight to patients as part of DED management that, although treatment leads to improvements in signs and symptoms, long-term treatment with a high level of compliance is required.[1] Furthermore, the patient and physician should agree on realistic expectations for disease management to ensure satisfaction and compliance with treatment.[1,16] In addition, it is important for patients to understand that some therapies take time to exert their full effects (typically 1–3 months, although sometimes longer for topical CsA); patient education on this topic improves compliance and reduces the risk of patient-driven treatment discontinuation. Therefore physicians should carefully monitor patient compliance during the early stages of treatment. Efficacy of the treatment should be assessed over a period of follow-up according to the expected time to onset of the treatment being used (e.g. 3–6 months for topical CsA).[1,5,16] Finally, healthcare professionals should discuss with patients the possible adverse events (AEs) associated with DED treatment, such as instillation-site pain and burning or stinging sensation after application of topical CsA. This effect has been reported in approximately 14–17% of patients across the different formulations of topical CsA ophthalmic emulsion. Patients should be encouraged to persist with their treatment because such events tend to be transient.[1,4,13,16,18] The rationale behind this is that hypoaesthesia is a common feature of DED as a result of corneal nerve damage, and treatment with topical CsA has been shown to increase nerve density, indicating corneal nerve regeneration.[19] This increase in corneal sensitivity may lead to the burning sensation upon instillation, which typically resolves after the first few months of treatment.

Long-term treatment with topical CsA CE 0.1% is associated with positive outcomes

The efficacy of topical CsA CE 0.1% for the treatment of moderate-to-severe and severe DED has been studied in two phase 3 randomised controlled trials, SICCANOVE and SANSIKA, involving more than 700 patients (Table 1).[20–23]

SICCANOVE study

In the SICCANOVE phase 3 double-blind study, 495 patients with persistent moderate-to-severe DED were randomised to receive either topical CsA CE 0.1% or vehicle for 6 months.[21] The mean corneal fluorescein staining (CFS) scores at baseline were 2.83 and 2.80 in the CsA CE 0.1% and vehicle groups, respectively. Notably, 85 of the 495 patients enrolled had a CFS score of 4 at baseline, indicating severe keratitis. Patients in the CsA CE 0.1% group had significant improvements from baseline in the objective part of the co-primary endpoint of DED signs (CFS) and symptoms (global visual analogue scale [VAS] scores) 6 months after treatment initiation (Figure 1). The difference between CsA CE 0.1% and vehicle was statistically significant for CFS as early as 1 month into treatment.

SANSIKA study

The SANSIKA phase 3 study evaluated the safety and efficacy of topical CsA CE 0.1% in 245 patients with severe DED over a 6-month period, followed by a 6-month and a subsequent 24-month open-label extension (OLE).[20,22,23] Severe DED was

Table 1. Ciclosporin A cationic emulsion 0.1% phase 3 trials in dry eye disease: study design and methodology.

Study name	SICCANOVE[21]	SANSIKA[20,22,23]
Study design	Multicentre, double-blind, randomised controlled trial	Multicentre, double-blind, randomised controlled trial followed by an open-label period
Number of patients	492	245
Treatment arms	CsA CE 0.1% (n = 242) Vehicle (n = 250)	CsA CE 0.1% (n = 154) Vehicle (n = 91)
Duration	6 months	6 months double-blind, followed by 6 months open-label then 24 months extension
DED severity	Moderate to severe	Severe
Primary endpoints	Change in CFS and change in global VAS score of ocular discomfort, unrelated to study treatment instillation, from baseline to Month 6	Combined CFS-OSDI responder rate at Month 6 (improvement of ≥2 grades in CFS from baseline and improvement of ≥30% in OSDI from baseline)
Key secondary endpoints	Lissamine green score Schirmer tear test (without anaesthesia) TBUT OSDI questionnaire Investigators' global evaluation	CFS OSDI Global VAS score of ocular discomfort Complete corneal clearing rate Lissamine green score

CFS, corneal fluorescein staining; CsA CE, ciclosporin A cationic emulsion; DED, dry eye disease; OSDI, Ocular Surface Disease Index; TBUT, tear film break-up time; VAS, visual analogue scale.

defined as a CFS score of 4 on the modified Oxford scale (from 0 to 5), a Schirmer test score of ≥2 mm/5 minutes and <10 mm/5 minutes and an Ocular Surface Disease Index (OSDI) score of ≥23.[23] Patients were randomised to receive one drop of CsA CE 0.1% or vehicle once daily for the first 6 months. All patients who subsequently continued into the 6-month OLE received CsA CE 0.1%. Therefore, the OLE part of this study comprised patients who received CsA CE 0.1% for 12 months (CsA/CsA) and patients who received vehicle for 6 months then switched to CsA treatment for 6 months (vehicle/CsA). After 12 months on study, patients were invited to participate in a further 24-month extension and received either CsA CE 0.1% or no treatment, depending on their clinical condition.

The 6-month results showed that CsA CE 0.1% was associated with an improvement in DED signs and symptoms, as evaluated by the primary composite endpoint of CFS-OSDI responder rate.[23] However, the effect with CsA CE 0.1% was not significantly greater than that of vehicle, with responder rates of 28.6% in the CsA CE 0.1% group and 23.1% in the vehicle group. The lack of superiority of CsA CE 0.1% over vehicle can be partly explained by several confounding factors. Firstly, the vehicle itself can potentially have a moderate but positive effect on DED symptoms and inflammation. Properties of the cationic nano-emulsion vehicle are such that it enhances tear film hydration, lubrication and stability, as well as reducing inflammation via inhibition of the protein kinase C pathway.[23,24] Secondly, the efficacy endpoint used in the study required a concomitant improvement in signs and symptoms. It is well documented that there is a weak correlation between signs and symptoms in DED for a given patient, and symptom severity and corneal sensation can be subjective.[23] Only 50% of patients in the study showed a concomitant change (improvement or worsening) in both signs and symptoms, which reduced the power of the statistical analysis.

The choice of the composite score as the primary endpoint may have decreased the power of the study by being too ambitious in such a multifactorial disease. A final consideration is the effect of topical CsA on corneal nerve regeneration.[19] The restoration of corneal sensitivity could

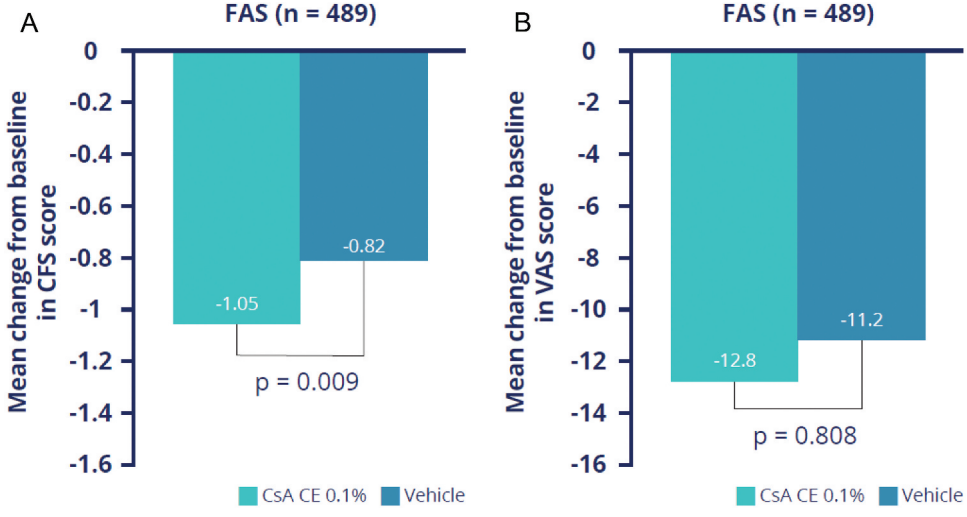

Figure 1. Change from baseline in co-primary endpoint after 6 months of treatment in the SICCANOVE study.[21] A: Mean change from baseline in CFS. B: Mean change from baseline in VAS scores.CFS, corneal fluorescein staining; CsA CE 0.1%, ciclosporin A cationic emulsion 0.1%; FAS, full analysis set; VAS, visual analogue scale.

lead to patients experiencing more discomfort during 3–6 months of treatment with CsA CE 0.1%, thereby reducing the likelihood of an improvement in the combined signs and symptoms score in this pivotal study.

Despite not reaching the primary endpoint during the randomised segment of the study, CsA CE 0.1% was shown to be effective in improving corneal surface damage and ocular surface inflammation, indicating an overall positive benefit–risk ratio after 6 months of treatment.[23] Notably, the likelihood of CFS improvement by at least three grades was approximately three times higher with CsA CE 0.1% than with vehicle, with 35.6% of patients in the CsA CE 0.1% group achieving grade 1 or less, compared with 14.5% in the vehicle group.

The analysis at 12 months of CsA CE 0.1% treatment showed that patients continued to experience improvements in DED signs and symptoms, including reduced CFS score, reduced human leukocyte antigen-antigen D-related cell-surface receptor (HLA-DR) expression, improved corneal clearing, and continuous improvements in global VAS and OSDI scores.[20] The results also demonstrated a continuous increase in the CFS-OSDI responder rate over the 12-month period (Figure 2), and an increase in the proportion of patients with complete corneal clearing. At Month 12, 12.5% of patients in the CsA/CsA group and 11.4% of patients in the vehicle/CsA group had a CFS score of 0. Overall, the 12-month results suggest a sustained effect of CsA CE 0.1% in patients with severe DED and indicate the value of continuing treatment for at least a 12-month duration.

In the 24-month OLE of SANSIKA (n = 66), patients continued receiving CsA CE 0.1%, with treatment being discontinued in patients who showed improvements in CFS scores to ≤2.[22] Based on that criteria, 62 patients discontinued CsA treatment, and the majority did not experience subsequent disease relapse during the 24-month follow-up, indicating sustained efficacy of CsA CE 0.1% (Figure 3). The estimated time to relapse was 32 weeks in patients who received 12 months of CsA CE 0.1% (CsA CE 0.1% /CsA CE 0.1%) and 25 weeks in those receiving CsA CE 0.1% for only 6 months (vehicle/CsA CE 0.1%). Furthermore, patients who had been treated with CsA CE 0.1% for 12 months were less likely to experience relapse compared with those who had received only 6 months of treatment, which indicates that control of the underlying pathogenetic factors of DED (i.e. downregulation of the ocular surface inflammation) was more pronounced with a longer treatment period (12 versus 6 months).

CsA CE 0.1% is well tolerated without systemic effects

An added benefit of using ophthalmic CsA CE 0.1% for managing DED is that, upon ocular administration, it does not result in systemic exposure due to negligible systemic absorption.[21,25,26] This is reflected by a low incidence of non-ocular adverse effects in clinical trials. Also of note is that there have been no significant safety findings associated with the conjunctiva in the two randomised controlled trials of CsA CE 0.1%.[20–23]

SICCANOVE study

CsA CE 0.1% was found to be well tolerated in the SICCANOVE study. The majority of the treatment-emergent AEs (TEAEs) reported were ocular in nature, and the most common TEAE was eye irritation (Table 2).[21] Although systemic TEAEs were reported in the SICCANOVE study, the majority were mild to moderate in intensity and they were considered to be unrelated

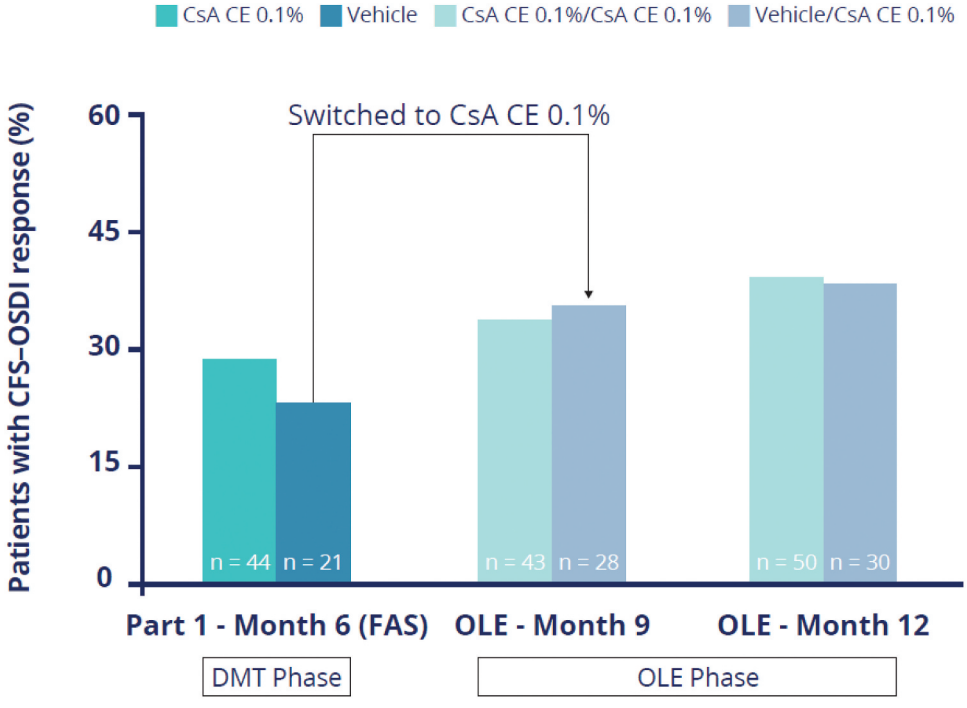

Figure 2. Corneal fluorescein staining–Ocular Surface Disease Index responder rates over 12 months in the SANSIKA study.[20]
CFS, corneal fluorescein staining; CsA CE 0.1%, ciclosporin A cationic emulsion 0.1%; DMT, double-masked treatment; FAS, full analysis set; OLE, open-label extension; OSDI, Ocular Surface Disease Index.

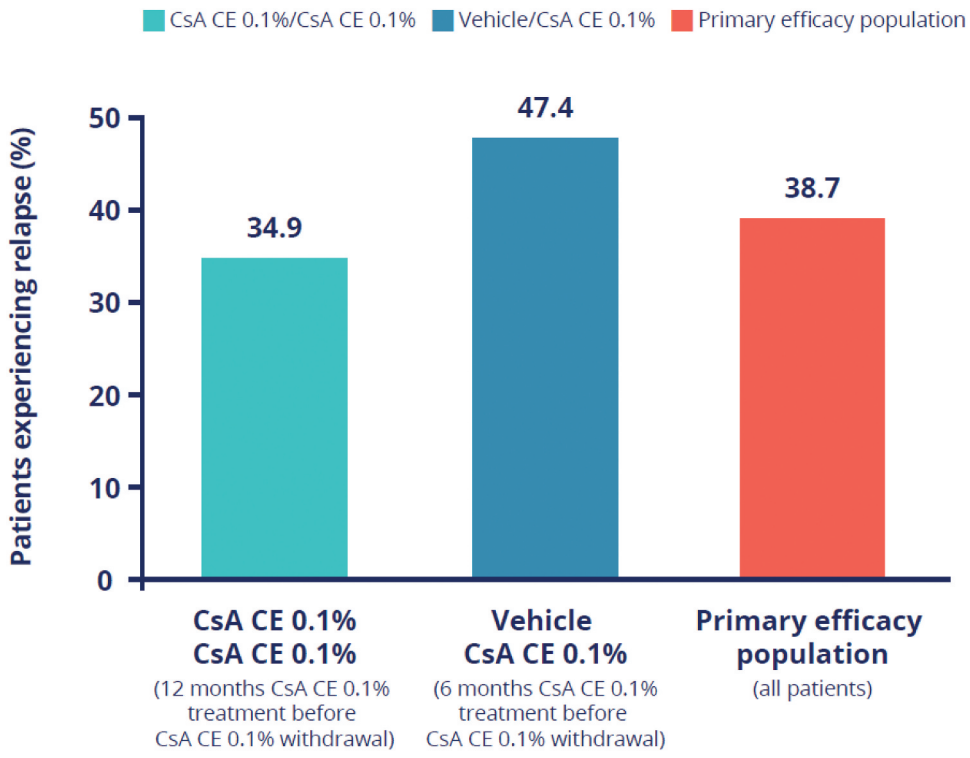

Figure 3. Relapse rates in markedly improved patients (corneal fluorescein staining score ≤2) during the 24-month SANSIKA open-label extension.[22]
CsA CE 0.1%, ciclosporin A cationic emulsion 0.1%.

Table 2. Ciclosporin A cationic emulsion 0.1% phase 3 trials in dry eye disease: key safety findings.

	SICCANOVE study[21]		SANSIKA study (6-month results)[20,23]	
Treatment-emergent adverse events	CsA CE 0.1% (n = 242)	Vehicle (n = 250)	CsA CE 0.1% (n = 154)	Vehicle (n = 90)
Ocular AEs, n (%)	103 (42.3)	67 (26.8)	66 (42.9)	27 (30.0)
Systemic AEs, n (%)	56 (23.1)	72 (28.8)	NR	NR
Treatment-related ocular AEs, n (%)	92 (38.0)	41 (16.4)	57 (37.0)	18 (20.0)
Ocular AEs leading to treatment discontinuation, n (%)	24 (9.9)	18 (7.2)	18 (11.7)	6 (6.7)
Most frequent treatment-related ocular AEs (%)	Eye irritation (16.1) Instillation-site irritation (9.1) Eye pain (7.0)	Eye irritation (2.4) Instillation-site irritation (1.6) Eye pain (2.8)	Instillation-site pain (29.2)	Instillation-site pain (8.9)
Treatment-related serious ocular AE, n (%)	1 (0.4)[a]	0	0	1[b]

AE, adverse event; CsA CE, ciclosporin A cationic emulsion; DED, dry eye disease; NR, not reported.
[a]One report of severe epithelial erosion of the cornea; resolved without sequelae.
[b]One report of severely reduced visual acuity.

to the study drug. There were only six reports of conjunctival hyperaemia associated with CsA CE 0.1% in the SICCANOVE study, versus three reports with vehicle.

SANSIKA study

The most frequently reported treatment-related ocular TEAE in the 6-month segment of the SANSIKA study was instillation-site pain, which was mostly mild in nature.[23] Similarly to SICCANOVE, after 6 months of treatment in the SANSIKA study, there were no findings to indicate systemic absorption of CsA. After 12 months of treatment, there were four reports of non-ocular TEAEs related to CsA CE 0.1% treatment in the 128 patients assessed.[20] These non-ocular TEAEs were stomatitis (1 patient), fatigue (1 patient), headache (1 patient) and increased upper airway secretion (1 patient).[20] There was only one report of allergic conjunctivitis in the 12-month SANSIKA findings, which occurred in the vehicle/CsA CE 0.1% group and was considered to be treatment-related.[20] CsA CE 0.1% was found to be well tolerated during the 24-month OLE, and no additional safety concerns were identified.[22] There was only one report of a treatment-related systemic AE (nasal congestion) and none of the AEs led to study discontinuation.

Which patients are best suited to receive topical CsA?

Due to the multifactorial nature of DED, it is not always clear which patients with the disease are the best candidates to treat with ophthalmic CsA preparations and who will have the highest likelihood of a good response.[4] Identifying

objective evidence of inflammation with biomarker testing may predict response to CsA treatment. Initial work on gene expression profiling in DED has identified correlations with HLA-DR, and these biomarkers may eventually enable identification of patients most likely to respond to specific treatments.[27] Although most studies of CsA CE 0.1% have primarily focussed on patients with severe DED, topical CsA may have a role in treating patients with moderate keratopathy, in order to reduce the risk of further entering the severe DED vicious circle. Specific data on this population are needed to determine if CsA CE 0.1% relieves DED signs and/or symptoms in the earlier stages of disease, and if it is also able to prevent disease progression to more severe forms of DED.

Some studies have shown that topical CsA treatment may be of similar benefit in subtypes of severe DED, such as DED associated with Sjögren's syndrome.[4] A pooled analysis of the SANSIKA and SICCANOVE studies identified that patients with severe DED, and those with Sjögren's syndrome and severe DED, were significantly more likely to be CFS-OSDI responders to CsA CE 0.1% treatment than to vehicle.[28] Although there was a trend towards a greater effect in patients with Sjögren's syndrome, this was not statistically significant. This finding indicates that CsA causes downregulation of inflammation, because Sjögren's is an autoimmune systemic disease. The pooled analysis also showed that the clinical benefits of CsA CE 0.1% were more pronounced in elderly patients (aged 65–74 years), female patients and menopausal patients, based on improvements in CFS score. There is other evidence to support the use of CsA in surgical settings, including after cataract surgery, glaucoma surgery and post-laser-assisted *in situ* keratomileusis (LASIK).[29] CsA may also have a role in the treatment of glaucoma therapy-related ocular surface disease, as shown by initial experimental and clinical evidence for reversal of its signs and symptoms.[25]

There is potentially a place for CsA CE 0.1% among patients in whom other CsA ophthalmic preparations have failed to produce a response. A small study of 40 patients with DED associated with Sjögren's syndrome, unresponsive to CsA anionic emulsion 0.05%, showed that switching to CsA CE 0.1% led to improvements in OSDI and Sjögren's International Collaborative Clinical Alliance (SICCA) ocular staining scores after 1 month and 3 months of treatment.[30]

How well does RWE with CsA CE 0.1% correlate with the randomised controlled trial data?

Although the phase 3 randomised controlled trials provided the pivotal data required to gain regulatory approval, the use of CsA CE 0.1% in the real-world setting can provide additional insights into how the evidence translates into clinical practice. Four published studies, involving more than 2000 patients with DED, have evaluated the use of CsA CE 0.1% in different clinical settings (Table 3).

French Authorisation for Temporary Use cohort

In a French compassionate-use programme (Authorisation for Temporary Use), 1212 patients with DED and severe keratitis received CsA CE 0.1% and were followed for 12 months; the mean treatment duration was 27.7 weeks.[31] Nearly all patients experienced improvement or stabilisation of their DED. A total of 42.1% and 48.6% of patients had improvement in keratitis signs and DED symptoms, respectively, at Month 12, whereas 45.7% and 45.0% of patients had stabilisation in signs and symptoms, respectively. Furthermore, 11.4% of patients and 6.4% of patients experienced a complete resolution of corneal damage and symptoms, respectively. The most common AEs were instillation-site pain and eye irritation, and no new or unexpected safety concerns were identified. The efficacy and safety findings from this RWE were noted to be consistent with the findings from the SANSIKA and SICCANOVE phase 3 studies, with similar degrees of improvements in signs and symptoms. Notably, the proportion of patients with complete corneal clearing in this real-world setting was a very similar proportion to that seen in clinical trials.

Scottish real-world experience

A Scottish study reported real-world experience of 52 patients with DED who were treated with CsA CE 0.1% for a mean duration of 11 months (range 2–30 months).[32] CsA CE 0.1% was well tolerated, and 88% of patients persisted successfully with treatment. Although six patients (11.5%) discontinued therapy due to intolerance, two were able to restart and persisted with treatment with CsA. The main reasons for treatment discontinuation were local irritation, burning or stinging. Data from this study support the long-term tolerability of CsA CE 0.1%, as seen in the SANSIKA and SICCANOVE studies.[20–23]

PERSPECTIVE study

The PERSPECTIVE non-interventional study prospectively evaluated the efficacy and safety of CsA CE 0.1% in 471 patients with DED and severe keratitis for a 12-month period, as part of routine clinical practice.[33] Patients were included from multiple centres in Finland, Germany, Norway, Sweden and the UK.[33] A significant reduction in CFS score from baseline was observed from as early as Week 4 and this was sustained through Month 12.[33] At baseline, the mean CFS sore was 2.56, and by Month 12, this score had decreased to 1.10.[33] The majority of patients (77.5%) experienced an improvement in CFS grade from baseline, and the majority of physicians rated CsA CE 0.1% as more effective than other medications.[33] There were significant improvements from baseline in the severity of subjective symptoms, VAS score and tear film break-up time.[33] Most physicians (80.4%) and patients (77.0%) rated the tolerability as 'good' or 'very good', with safety data being consistent with the known safety profile of CsA CE 0.1%.[33] The authors concluded that, in routine clinical practice, CsA CE 0.1% demonstrated statistically significant reductions in the severity of signs and symptoms of DED.[33]

Table 3. Real-world studies of ciclosporin A cationic emulsion 0.1% in dry eye disease.

Study/setting	French ATU[31]	Scottish real-world experience[32]	PERSPECTIVE European study[33]	English real-world experience[34,35]
Study design	Compassionate-use programme	Retrospective chart review	Prospective non-interventional clinical study	Retrospective study
Number of patients	1212	52	471	463 (322 with DED)
Duration	12 months	11 months (mean)	12 months	14.6 months (mean)
DED severity	DED with severe keratitis	NR	DED with severe keratitis	NR
Key efficacy results	42.1% and 48.6% of patients had improvements in signs and symptoms, respectively, at Week 12	88% of patients persisted with treatment	Mean reduction of CFS grade of 1.42 from baseline at Month 12 Significant reduction in CFS grade from Week 4 and at all time points (secondary endpoint)	82% of patients with DED had resolved or stable disease (treatment success)
Key safety results	Instillation-site pain occurred in 10.8% Eye irritation occurred in 8.2%	7.7% discontinued treatment due to intolerance (local irritation, burning, stinging)	Patients and physicians reported their assessment of tolerability with the study medication using a four-point scale (very good, good, satisfactory, poor) 77.0% of patients rated tolerability as good or very good. 15.7% rated tolerability as satisfactory and 7.3% rated tolerability as poor	11.5% discontinued treatment due to intolerance (burning or discomfort)

ATU, Authorisation for Temporary Use; DED, dry eye disease; NR, not reported.

Real-world experience of CsA in ocular surface inflammatory diseases in England

A retrospective study was conducted in England to report on the real-world experience of CsA CE 0.1% among 463 patients with ocular surface inflammatory diseases, including DED, allergic eye disease (including VKC and atopic keratoconjunctivitis), ocular mucous membrane pemphigoid and Stevens–Johnson syndrome.[34] The majority of patients had a diagnosis of DED (n = 322) and the mean follow-up duration was 14.6 months.[34] Efficacy was shown to be highest among patients with DED, with 82% of patients considered to experience treatment success after a mean treatment duration of 12.1 months.[34] In this study, treatment success was defined as the resolution of signs and symptoms (30.4% of patients) or stable disease (51.6%).[34] Intolerable AEs (burning sensation and discomfort) leading to treatment withdrawal were reported in 11.5% of patients with DED.[34] This study demonstrated tolerability results comparable to those reported in the SANSIKA study.[34] The investigators recommend that all non-infective chronic ocular surface inflammatory diseases should be treated with a short course of topical steroids followed by topical CsA.[34]

Discussion

The available literature indicates that the use of topical CsA CE 0.1% is well tolerated and effective for long-term use in DED, and that treatment periods of up to 12 months continue to provide benefit to patients. Long-term efficacy and safety data are supported by findings from randomised controlled trials as well as RWE.

Improvements in clinical signs (CFS score) and symptoms may be evident from as early as 4 weeks after CsA CE 0.1% treatment initiation; nevertheless, patients should be encouraged to persist with therapy as these improvements may take longer to occur and/or may intensify over time. A proportion of patients (~12%) may experience complete healing of keratopathy after long-term (12 months) treatment, including those who had severe disease at baseline. The data support the concept that CsA CE 0.1% is potentially disease-modifying, as up to 65% of patients do not experience disease relapse after treatment cessation.

The evidence so far indicates that patients with severe DED appear to benefit the most from CsA CE 0.1%, including those with underlying Sjögren's syndrome. Further data are needed to support its use in patients with less-severe disease.

Overall, CsA CE 0.1% is well tolerated: the most common AEs are local ocular effects, such as burning sensation, pain and irritation in the eye after instillation. Real-world data suggest that approximately 12% of patients may discontinue treatment due to these effects, a percentage similar to that observed with other formulations of topical CsA. For this reason, before treatment initiation with topical CsA, patients should be informed about potential related AEs, such as pain and burning/stinging sensation upon instillation. Physicians should encourage patients to persist with their treatment because these symptoms are usually transient and improve as the ocular surface improves. It is also important to reassure patients that topical CsA has almost no systemic absorption and therefore the risk of systemic AEs is minimal.

In addition to managing DED, CsA CE 0.1% has also demonstrated efficacy in the treatment of VKC. Usually presenting in children, VKC is characterised by allergic inflammation of the ocular surface mediated by T-helper 2 and other immune cells; therefore, CsA is an ideal anti-inflammatory agent to use in this setting.[14,15] Results from the VEKTIS study provide further evidence for the beneficial effects of CsA CE 0.1% on corneal healing. In addition, the safety profile of CsA CE 0.1% in the paediatric VKC setting is consistent with the DED setting.[14,15] In the VEKTIS 12-month study, the most common TEAE was instillation-site pain, and only one patient discontinued treatment due to a TEAE.[15] There were no unexpected safety findings, even in the group receiving high-dose CsA CE 0.1%.[15]

Key take-home messages

- Clinicians treating patients with severe DED can prescribe CsA CE 0.1% for periods of 12 months or more and expect sustained benefits with minimal adverse effects
- Patient education is important to ensure compliance with therapy for maximal effect, especially during the early stages of treatment, due to potential lag time to improvement onset
- Patients should be aware of the common AEs, such as burning, pain and irritation upon instillation, and that these are typically transient; they should also be reassured that topical CsA has almost no systemic absorption

Disclosures of interest

ML has received grant support from Théa Pharma GmbH; consulting fees from Pharm-Allergan, Alcon/Novartis, DMG Pharma, GlaxoSmithKline, Horus Pharma, Quantel Medical, Santen, Shire/Takeda, Théa Pharma GmbH, and TopiVert Pharma; meeting and travel support from Théa Pharma Gmb, Santen, and Alcon/Novartis; honoraria for participation in data safety monitoring boards/advisory boards from Pharm-Allergan, Alcon/Novartis, DMG Pharma, GlaxoSmithKline, Horus Pharma, Quantel Medical, Santen, Shire/Takeda, Théa Pharma GmbH, and TopiVert Pharma. **AL** has received consulting fees from Santen; honoraria for participation in lectures, presentations and speakers bureaus or educational events from Santen, URSAPHARM, Théa Pharma GmbH, and Alcon/Novartis. **PJP** has no financial interests to disclose. **CB** has received grant support from Santen, Théa Pharma GmbH and Horus Pharma; consulting fees for Pharm-Allergan, Alcon/Novartis, Horus Pharma, Santen and Théa Pharma GmbH.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This review was funded by Santen SA. Ana Tadeu of OPEN Health Communications (London, UK) provided writing, editorial, and formatting support, which was contracted and funded by Santen SA.

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