Tolerance and Adherence to Cationic 0.1% Cyclosporine in Ocular Graft-versus-Host Disease

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Keywords

Ocular graft-versus-host disease · Dry eye disease · Topical cyclosporine · Intolerance · Cationic formulation

Abstract

Introduction: Anti-inflammatory, topical therapy of severe keratitis in dry eye disease (DED) and ocular graft-versus-host disease (oGvHD) includes steroids, cyclosporine (Cs), and others. In Germany, a commercial product containing 0.1% Cs in a cationic formulation is available since 2015. **Objective:** The aim of this study was to present real-life data using cationic 0.1% Cs in oGvHD patients. **Methods:** This was a retrospective study of 26 oGvHD and 41 DED patients with corneal staining of at least Oxford grade III. Parameters analyzed were Ocular Surface Disease Index, corneal staining, intraocular pressure, tear film break-up time, Schirmer, and visual acuity. In addition, it was evaluated how different Cs formulations were tolerated. **Results:** Corneal staining improved significantly in 1 eye in DED but not in oGvHD. In DED, cationic 0.1% Cs was not tolerated by 32% of the patients, in contrast to 0.05% Cs in castor oil not tolerated by 47% and liposomal 0.05% Cs by 63%. In oGvHD patients, cationic 0.1% Cs was not tolerated by 62%, 0.05% Cs in castor oil by 33%, and liposomal 0.05% Cs by 39% of the patients. **Conclusions:** This study demonstrates differences between

the tolerance of different Cs formulations depending on the underlying cause of severe keratitis. Cationic 0.1% Cs is considerably less tolerated in oGvHD, and its use should be considered with care.

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Introduction

Dry eye disease (DED) is a complex pathology of the ocular surface that affects millions of individuals [1]. In addition to supplementation of tear components, treatment of lid margin disease including meibomian gland disease and augmentation of ocular surface exposure to adverse environmental conditions, a key therapeutic component is the reduction of ocular surface inflammation [2]. From animal models simulating different forms of DED [3] and from numerous retrospective and prospective clinical trials, it can be concluded that one of the most important pathomechanisms of the proposed vicious circle of DED [4] is the generation of autoreactive T-cells, mainly of the Th17 and the Th1 phenotype. It is well established and generally accepted that still unknown

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autoantigens are exposed by occurring ocular surface insults and lead to complex immunological mechanisms that include the ocular surface immune system as well as regional lymph nodes [5]. This afferent immune reaction eventually leads to an efferent immune response at the very site of the initial insult. Therapeutic approaches aim to interrupt this immune response through artificial tears and topical anti-inflammatory substances such as corticosteroids. These are often applied with tapering intensity but may feature potential side effects such as cataract promotion and elevation of eye pressure [6–10]. As an alternative to corticosteroids, cyclosporine (Cs) was shown to be effective in treating DED by reducing inflammation-associated signs such as corneal fluorescein staining and by increasing tear secretion [11, 12]. Since then, Cs has been applied in large numbers of patients without severe side effects such as frequently reported staining and burning sensations at the instillation site [12–14].

Since, until 2015, no topical Cs product was approved in Europe, formulations could only be applied through local pharmacies, using carriers such as castor oil, mineral oils, peanut oil, and so on, however with only very limited evidence from clinical trials and with varying concentrations of 0.05–2% of Cs [11, 15–17].

In 2015, a first Cs product was approved by the European Medical Agency (EMA) for treating DED. The product (Ikervis[®], Santen, Munich, Germany) contains 0.1% Cs, formulated using a cationic basis of cetalkonium chloride, which had already been introduced as main part of an artificial tears product (Cationorm[®], Santen). Based on the clinical trials that were conducted prior to market launch, approval by the EMA was granted for severe keratitis only in adult dry eye patients that were refractive to previous dry eye therapy [18, 19].

In this retrospective study, we wanted to analyze clinical data on the use of the novel Cs formulation in patients with severe keratitis that were refractory to previous topical dry eye therapy. In this analysis, we especially focused on tolerance and adherence to 0.1% Cs in ocular graft-versus-host disease (oGvHD), which shows distinct features of dry eye disease and often presents with severe keratitis.

Methods

Patients

Clinical data was retrospectively analyzed from all patients suffering from DED or oGvHD which were treated at the Department for Ophthalmology of the University of Cologne, Cologne, Germany, between July 2015 and December 2016 with the then novel

commercially available 0.1% Cs A formulation (Ikervis[®]; Santen, Munich, Germany) due to severe keratitis and DED refractive to therapy. Data were collected from patients presenting at least twice in the study period. In our clinic, severe keratitis was defined as corneal fluorescein staining $\geq$ grade III on the Oxford scale. Clinical parameters assessed were Ocular Surface Disease Index (OSDI) score, corneal fluorescein staining, intraocular pressure (IOP), tear film break-up time (TFBUT), Schirmer's Test I (without topical anesthesia) and best spectacle-corrected visual acuity (BSCVA). In addition, in case of discomfort during treatment, it was evaluated why the application was discontinued and how other Cs formulations were tolerated if applied previously (e.g., formulations based on castor oil, liposomal or imported Cs 0.05% Restasis[®] (Allergan Inc., Dublin, Ireland). All our patients receiving any Cs containing eye drops (pharmacy formulations, Ikervis[®], Restasis[®]) are by standard informed about possible stinging sensation to increase adherence to this therapy. For this study, intolerance to topical Cs was hereby defined as self-reported discontinuation of application due to local irritation. Details on reported drug-related symptoms were collected from patient files, if specifically reported.

Pharmacy Formulated Cs-Containing Eye Drops

0.05% Cs in Castor Oil

Formulation of 0.05% Cs in castor oil was performed at a pharmacy as follows: 0.05% w/v Cs A was stirred in heat-sterilized castor oil (2 h, 160 °C) alone or in combination with medium chained triglycerides (oleum neutrale) until completely solved. Emulsion was sterile filtered (0.2 μ m filter) and filled in sterile 10 mL vials for use.

0.05% Liposomal Cs

Formulation of 0.05% liposomal Cs was performed following a modified protocol patented previously (EP 0 945 136 A1) using lecithin, glycerol, and cyclosporine A. Formulation was filled in sterile 10 mL vials for use.

Subgroup Analysis

Patient groups consisted of either patients receiving 0.1% cationic Cs as first-time Cs application or of patients that had other Cs formulations previously and who (i) did not tolerate other Cs or (ii) did tolerate other Cs, demonstrated corneal staining $\geq$ grade III in at least 1 eye and were switched to 0.1% cationic Cs to avoid continuing an “off-label” application.

The following data sets were used for tolerance analyses: (i) all patients, (ii) patients with chronic oGvHD, (iii) patients with DED other than oGvHD (in the following termed DED).

For efficacy analysis, only patients that tolerated 0.1% cationic Cs were analyzed.

Furthermore, tolerance of 0.1% cationic Cs was compared to tolerance of previously applied Cs formulations.

Statistical Analysis

Only patients tolerating 0.1% cationic Cs were included in statistical analysis regarding efficacy, and subgroups consisted of DED and oGvHD patients, respectively. For statistical analysis, data were always analyzed with respect to their Gaussian distribution using the Kolmogorov-Smirnov test, followed by either parametric or non-parametric test. To compare clinical parameters (BSCVA, Schirmer's, staining, TFBUT, IOP, OSDI) of left and right eye (OD and OS) prior to treatment with 0.1% cationic Cs,

either Student *t* test for unpaired samples or Mann-Whitney U test was used. To compare the efficacy of 0.1% cationic Cs treatment, clinical data before and after 0.1% cationic Cs treatment were analyzed using either Student *t* test for paired samples or the Wilcoxon test. A *p* value ≤ 0.05 was considered to be significant.

For further subgroup evaluation, patients receiving 0.1% cationic Cs without previous topical Cs were analyzed. Additionally, eyes of 0.1% cationic Cs-tolerating patients were divided into corneal staining grade 3, grade 4, or grade 5 and analyzed for efficacy. For both analyses, the Wilcoxon test was used.

Boxplots represent median $\pm$ 25–75% percentile. Whiskers indicate the lowest and highest value without outliers (circle). Mean $\pm$ SD, and range (minimum–maximum) are depicted below each boxplot. Statistical analysis was performed using commercially available software (SPSS version 25; IBM, Armonk, NY, USA).

Results

Demographics

Sixty-seven patients (female: 41, male: 26, age: 61 ± 16 years, range: 24–85 years) were included in the following analysis, including 26 chronic oGvHD, NIH grade III patients (female: 8, male: 18, age 52 ± 13 years, range: 27–70 years) and 41 DED patients (female: 33, male: 8, age 55 ± 18 years, range: 24–85 years; Table 1). For a detailed list of diagnoses in DED patients see online suppl. Table 1 (see www.karger.com/doi/10.1159/000509034 for all online suppl. material).

Clinical Parameters before 0.1% Cationic Cs

Average best corrected visual acuity (BCVA) of all patients was 0.3 ± 0 logMAR (OD) and 0.2 ± 0.3 logMAR (OS) before 0.1% cationic Cs, in DED patients BCVA was 0.3 ± 0.5 (OD) and 0.2 ± 0.3 (OS), for oGvHD 0.2 ± 0.3 (OD) and 0.3 ± 0.3 (OS). The Schirmer test without anesthesia was reduced in all groups. Average Schirmer's was 7.2 ± 8.8 mm (OD) and 6.2 ± 7.9 mm (OS) in all patients. In DED patients Schirmer's was 8.8 ± 10.0 mm (OD)/ 6.8 ± 6.9 mm (OS) and in oGvHD patients 5.1 ± 6.5 mm (OD)/ 5.4 ± 8.8 mm (OS). The corneal fluorescein staining score was increased in all patients (3.2 ± 1.2 [OD]/ 3.2 ± 1.0 [OS]). Average staining in DED patients was 3.1 ± 1.1 (OD) and 3.1 ± 0.8 (OS). oGvHD patients had an average staining of 3.5 ± 1.4 (OD) and 3.4 ± 1.3 (OS). TFBUT was 2.4 ± 2.3 s (OD)/ 2.2 ± 2.3 s (OS) in all patients. DED patients showed a TFBUT of 2.3 ± 2.1 s (OD) and 2.5 ± 2.1 s (OS), whereas oGvHD patients had a TFBUT of 1.9 ± 2.1 s (OD) and 1.9 ± 2.2 s (OS). IOP in all patients was 14.3 ± 4.4 mm Hg (OD) and 14.4 ± 4.1 mm Hg (OS), in DED patients 14.3 ± 4.1 mm Hg (OD) and 14.3 ± 3.9 mm Hg (OS), in oGvHD patients 14.3 ± 5.0 mm Hg (OD) and

Table 1. Demographic data on the full patient data set

	N	Age, years		Gender, n	
		mean $\pm$ SD	range	female	male
All patients	67	61 ± 16	30–92	41	26
DED patients	41	55 ± 18	24–85	33	8
oGvHD patients	26	52 ± 13	27–70	8	18

14.6 ± 3.7 mm Hg (OS). IOP in all patients was 14.3 ± 4.4 mm Hg (OD) and 14.4 ± 4.1 mm Hg (OS), in DED patients 14.3 ± 4.1 mm Hg (OD) and 14.3 ± 3.9 mm Hg (OS), in oGvHD patients 14.3 ± 5.0 mm Hg (OD) and 14.6 ± 3.7 mm Hg (OS). OSDI values were increased in all patients (62 ± 23), with comparable OSDI in DED patients (64 ± 23) and oGvHD patients (60 ± 25).

All results are depicted as boxplots in online supplementary Figure 1. Based on NIH consensus criteria, eye scoring is performed in all patients presenting to our clinic. Here, all oGvHD patients included in this analysis received score 3 according to severe dry eye symptoms significantly affecting activities of daily living and accompanied with loss of vision caused by keratoconjunctivitis sicca [20].

Concomitant Therapy

During the study period, all patients used artificial tear products. Also, several ointments were applied (VitApos[®], Ursapharm; Bepanthen[®], Bayer; Corneregel[®], Bausch & Lomb). Forty-one patients were treated in parallel with topical glucocorticoids (Monodex[®], Théa Pharm; Dexapos comod[®], Ursapharm; Dexasine[®], Novartis; Vexol[®] Alcon), 14 patients also with autologous serum eye drops, and 2 patients with 5% albumin eye drops. Furthermore, 4 DED patients also used anti-allergic eye drops (Zadithen ophtha sine, Théa Pharma; Berberil[®]-N, Bausch&Lomb), 3 patients were treated with Monoprost[®] (Théa Pharm) or Taflotan[®] (Kohlpharma), and 1 patient temporarily received Floxal[®] (Bausch&Lomb). Additionally, the following concomitant ocular treatments were documented: 5 DED patients had punctum plugs, 37 patients performed lid margin hygiene, 7 patients wore therapeutic contact lenses. For a more detailed overview, see Table 2.

Tolerance/Intolerance Analysis

The average follow-up for all patients was 120 ± 81 days (range 2–485 days).

Table 2. Number of patients using additional ophthalmological treatments or therapy besides topical Cs in the study period

	Steroids, <i>n</i>	ASED ^a , <i>n</i>	Ointments, <i>n</i>	Anti-allergic, <i>n</i>	Lid hygiene, <i>n</i>	Punctum plugs, <i>n</i>	TCL ^b , <i>n</i>
All patients	41	16	26	4	37	5	7
DED patients	21	7	16	4	22	5	5
oGvHD patients	20	9	10	0	15	0	2

^a Autologous serum/albumin eye drops. ^b Therapeutic contact lenses.

Fig. 1. Percentage of all patients with intolerance to different Cs formulations.

Intolerance due to side effects with consecutive discontinuation of 0.1% cationic Cs developed in 44% of all treated patients versus 39% that developed intolerance to 0.05% Cs in castor oil, 47% to 0.05% liposomal Cs, and 0% to commercial 0.05% Cs (Restasis®; Fig. 1).

Analyzing oGvHD versus DED subgroups, 32% of the patients with DED discontinued 0.1% cationic Cs, 47% discontinued 0.05% Cs in castor oil, and in 63%, 0.05% Cs as liposomal formulation was not tolerated (Fig. 2). In oGvHD, 62% of the patients discontinued 0.1% cationic Cs, 38% discontinued castor oil Cs, 33% discontinued liposomal Cs, and all related patients tolerated Restasis®.

Symptoms leading to discontinuation in DED patients were burning sensations in 67%, redness in 22%, and itching in 14%. In the oGvHD group, 59% of the patients who stopped the treatment reported about burning sensa-

tions, 29% about redness, 8% about conjunctival and lid swelling, and 4% about itching (Fig. 3).

Furthermore, the tolerance of 0.1% cationic Cs was compared to tolerance of previously applied Cs formulations. Seven of the DED patients tolerated 0.1% cationic Cs better than castor oil and liposomal formulations, but only 3 DED patients tolerated 0.05% Cs in castor oil better than 0.1% cationic Cs. In contrast, 9 of the oGvHD patients tolerated 0.1% cationic Cs less than previous applied Cs in castor oil or liposomal formulations or Restasis®. Only 2 oGvHD patients tolerated 0.1% cationic Cs better than previous applied Cs formulations.

Efficacy Analysis

For the following analysis of efficacy of 0.1% cationic Cs, only patients tolerating the therapy were included. Average time of application of 0.1% cationic Cs in those

Fig. 2. Intolerance to different Cs formulations in oGvHD (**a**) and DED (**b**) patients.

Fig. 3. Distribution of described side effects in the study groups, leading to the discontinuation of 0.1% cationic Cs.

patients was 141 ± 85 days (range 30–485); 137 ± 68 days (range 30–287) in the DED group and 151 ± 123 days (range 35–458) in the group with oGvHD.

Fifteen patients (female: 7, male: 8, age: 49 ± 17 years, range: 24–78 years) were included for the following sub-analysis, with 12 DED patients (female: 7, male: 5, age 49 ± 18 years, range 24–78 years) and 3 oGvHD patients (female: 0, male: 3, age 51 ± 15 years, range 35–65 years) receiving 0.1% cationic Cs as first Cs treatment.

There were no significant changes in BSCVA, Schirmmer test I, TFBUT, and OSDI scores but a significant reduction of corneal staining of the right eye in the DED group

and a significant reduction of IOP of the left eye in the oGvHD group after the observed period of 0.1% cationic Cs application (online suppl. Fig. 2–7).

Discussion

Topical application of Cs is a well-established therapy for DED including chronic oGvHD. New formulations are constantly developed and tested, and one formulation based on a cationic drug-delivery system was recently approved and marketed in the EU. Besides varying data

from clinical trials on the efficacy of topical Cs and potential carrier effects, tolerance plays a major role in the adherence of patients to Cs. This is particularly important, as often enough patients require therapy over years, especially if chronic inflammatory diseases such as Sjögren syndrome or oGvHD are the cause of dry-eye disease signs and symptoms.

The retrospective analysis presented here was performed following marketing of the cationic based 0.1% Cs formulation using data from a specialized outpatient clinic on DED and oGvHD.

As the main finding, this retrospective analysis shows equal intolerance rates for the cationic Cs in DED in comparison to both published clinical trials [18, 19, 21, 22]. Another retrospective study reported tolerance in 88% of the 52 DED patients included and a successful therapy after an average treatment with 0.1% cationic Cs of 11 months [23].

The SICCANOVE and SANSIKA trials registered pain sensation during installation in 30–54% of the DED study patients but suggested a decrease in ocular surface irritation with a continuing application of 0.1% cationic Cs [18, 19]. Intolerance in this study under real-life conditions was defined as side effects leading to drug discontinuation in contrast to the published prospective trials that defined intolerance as occurring side effects. We made the definition for this analysis more specific, as almost all of our patients report some stinging effects using Cs, and we are aware of the situation that patients in trials often demonstrate higher adherence to therapy and might accept different levels of side effects, which make a direct comparison difficult.

Although applied with the same criteria as in DED patients, we noted an increased intolerance rate for 0.1% cationic Cs in over 60% of the oGvHD group, whereas DED patients demonstrated a highly increased intolerance rate of up to 63% for pharmacy-based formulations. This points out that although indication criteria are similar, differences have to be made between disease entities. Patients with chronic oGvHD are likely to depict extensive inflammatory activity and advanced epithelial pathology, in particular of the conjunctiva. Therefore, although demonstrating severe keratitis that implies the use of cationic Cs, the extent of conjunctival or lid disease specifically in oGvHD may be the reason for severe stinging and intolerable side effects. To our knowledge, no correlations have until now been made between these factors to be able to predict topical eye drop tolerance. Therefore, we propose for chronic ocular GvHD, that cationic Cs be applied with

increased awareness according to the warnings and precautions included in the summary of product characteristics, in particular if applied with concomitant medication. Ideally, prospective randomized clinical trials should be performed in chronic ocular GvHD to increase evidence for using cationic Cs in the entity and to allow a better assessment with regard to on- or off-label use, which is debatable in this case.

Most discontinuing patients quit the treatment due to severe burning sensations after application of topical Cs. In this context, the carrier of the active substance might be one of the confounding factors. We hypothesize that the interaction of carrier substances and the active mediates intolerance reactions as carrier substances applied as part of artificial tears (Cationorm® or OptivePlus®) have not been reported to induce side effects at the same rates [24, 25]. As pointed out above, the role of conjunctival and lid epithelium in this context requires investigation together with pharmacological interactions between concomitantly applied drugs. These findings underline the importance of the development and testing of pharmacologically unirritating carrier molecules for Cs applications. Here, innovative microemulsion systems (MiDROPS, EyeCRO), sorbitan ester nanoparticles, or micelles as potential delivery systems to apply Cs to the ocular surface [26–28], but also novel carrier molecules like semifluorinated alkanes [29–31], could facilitate a longer-lasting and less irritating release of Cs at the ocular surface [32].

There are several limitations to this study, which are due to its retrospective nature. They include a limited number of patients and a broad variation of concomitant therapies including previous Cs applications that may have led to sensitization of the ocular surface. There is certainly a need for reports of long-term experience, which in the case of cationic Cs now approaches 5 years of marketing. It will be very interesting to see experiences from other centers, in particular if focus is placed on clinical findings beyond keratitis and tear parameters such as extent of inflammatory activity, conjunctival disease, and lid margin pathology. Regarding regulatory aspects, detailed reporting of suspected adverse effects after authorization and marketing of new medicinal products is strongly emphasized to allow continued monitoring of the benefit-to-risk ratio. Based on this retrospective analysis, our current standard of care with regard to chronic oGvHD includes the first-line application of cationic 0.1% Cs (Ikervis®) under increased awareness in patients with severe keratitis (Oxford corneal staining ≥ 3), and for patients with less staining the use of pharmacy-based formulations or Restasis®.

Statement of Ethics

This retrospective study adhered to the Declaration from Helsinki and was in conformity with the regulations of the local Ethics Committee (Ethics Committee of the University Hospital of Cologne, Cologne, Germany, 16-405, 13-307).

Conflict of Interest Statement

U.G. and S.S. have no conflicts of interest. P.S. has received financial support from Novaliq GmbH and Roche, and honoraria from Santen, URSAPHARM Arzneimittel GmbH, and Bausch & Lomb.

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Author Contributions

U.G. analyzed data and wrote the manuscript. S.S. collected patient data and wrote the manuscript. P.S. designed the study, collected patient data, and wrote the manuscript.

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