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Research Article

Comparison of the Clinical Efficacy of Three Different Eye Drops for the Treatment of Dry Eye

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Abstract

Purpose: To compare the safety and efficacy of perfluorohexyloctane and water-based lipid-containing eyedrops.

Methods: Prospective, randomized, comparative, open label clinical trial in patients with evaporative dry eye due to Meibomian gland dysfunction (MGD). Group 1 was treated with EvoTears® (URSAPHARM), group 2 with Cationorm®MD sine (Santen), and group 3 with Systane® Balance (Alcon). Changes in terms of non-invasive break-up time (NIBUT), tear film lipid layer thickness (LLT), slit lamp examination and subjective symptoms were evaluated during a 28-day follow-up.

Results: Each group comprised 10 patients. Statistically significant improvements in NIBUT were found in all groups ($p < 0.001$), with a larger percentual increase with EvoTears® at day 28 vs baseline (+121.3%). Patients treated with EvoTears® had less corneal staining than patients with Systane® Balance treatment ($p = 0.007$) at day 28. In all groups, significant changes in the expression of Meibomian glands, quality score of Meibomian secretion, level of conjunctival hyperemia and corneal staining were found ($p < 0.001$). In all groups, a significant improvement of symptoms evaluated by the ocular surface disease index (OSDI) was also observed ($p = 0.008$). The patients and the investigator scored efficacy and tolerability as acceptable or very good in all groups.

Conclusion: EvoTears® showed a tendency for better outcomes in nearly all test parameters: improved tear film (NIBUT), ocular surface (staining), and most of all subjective impressions of MGD patients (OSDI) and is a suitable option to treat evaporative dry eyes. The results allow to start a discussion about a stable lipid layer is more important than a thick lipid layer.

Keywords: *Dry Eye Disease; Meibomian Gland Dysfunction; Semifluorinated Alkanes; Tear Film; Lipid Layer Thickness; Perfluorohexyloctane*

Introduction

The Dry Eye Workshop (DEWS I and II) of the Tear Film and Ocular Surface Society (TFOS) distinguishes 2 different types of dry eye disease (DED): hyposecretory (tear-deficient) and hyperevaporative (evaporative) [1,2]. Tear-deficient or hyposecretory DED is generated by a deficiency in aqueous/mucinous production, whereas hyperevaporative DED is characterized by a disturbed lipid layer and therefore associated with Meibomian gland dysfunction (MGD) [2]. Both types frequently occur in combination rather than as separate modalities, and therefore mixed forms can be also present [2]. In all modalities of DED, the central pathophysiological mechanism is the loss of tear film homeostasis [2]. This leads to tear film instability, with break-up time (BUT) values that may drop below 10 seconds (s)

even in mild cases of DED. This instability in moderate and advanced cases can generate frequent dry spots on the ocular surface between blinks, affecting the morphology and functionality of the corneal epithelium [3].

The use of tear film substitutes is the most common treatment prescribed for DED and MGD, which has no pharmacological effects in terms of stimulation [4]. Different types of eye drops, eye gels and eye ointments have been developed and commercially released to substitute different layers of the tear film [4]. The main component of lubricating eye drops is water which is combined with viscosity enhancing polymers, such as hyaluronic acid (HA), hydroxypropyl methylcellulose (HPMC) or polyvidone [5]. These chemically inert molecules substitute the aqueous/mucinous layer of the tear film, binding physically to the ocular surface and increasing the retention time of water molecules. Likewise, a substitution of the lipid layer can be also promoted by adding lipophilic substances, such as mineral oil or phospholipids [5]. One of the disadvantages of lipid-containing eye drop solutions is the content of emulsifying agents and preservatives, such as benzalkonium chloride (BAC), which may be toxic to the ocular surface unless they are filled into specific multidose containers that prevent from any microbiological contamination from outside [6].

A lipophilic alternative to watery eye drops is perfluorohexyloctane (EvoTears®, URSAPHARM Arzneimittel GmbH). This aliphatic, partly fluorized hydrocarbon acts as a nonblurring lubricating agent for the ocular surface and needs no preservative as it does not contain water [7].

To date, clinical data, evaluating the effect of these eye drops have shown that they increase TBUT and also lead to a decreased corneal staining within weeks [8,9]. To our knowledge, no direct comparisons between water-based and water-free eye drops for DED and MGD therapy have been published yet.

Objective of the Study

The objective of the present clinical trial was to evaluate the effect of perfluorohexyloctane-based drops (EvoTears®) on the ocular surface after 28 days of application and to compare it with the effect achieved with two water-based eye drops (Systane® Balance and Cationorm® MD sine).

Material and Methods

Subjects and ethics statement

Monocentered, prospective, randomized, comparative open clinical trial comprising 30 patients with evaporative DED due to mild to moderate MGD (https://www.isrctn.com/, identifier ISRCTN15512057). The patients were randomized to the following groups: group 1 including 10 patients treated with EvoTears® eye drops (URSAPHARM Arzneimittel GmbH, Saarbrücken, Germany), group 2 including 10 patients treated with Cationorm® MD sine eye drops (Santen Pharmaceutical Co. Ltd, Osaka, Japan), and group 3 including 10 patients treated with Systane® Balance eye drops (Alcon, Fort Worth, Texas, USA). All patients were informed about the study and provided informed consent. The study was performed in accordance with the tenets of the Declaration of Helsinki and power analysis was performed to justify the number of patients enrolled in the study. Likewise, the study received the approval of the local ethics committee.

Randomization numbers were used to assign patients to each the three eye drop treatment groups. Due to the open trial design, it was evident for the investigator and for the patient, whether EvoTears®, Cationorm® MD sine or Systane® Balance was applied. Male and female patients with at least 18 years of age were included in the study, with evaporative dry eye and mild to moderate MGD [defined as the presence of hyposecretion and reduced manual expression of Meibomian glands, NIBUT < 10s and a staining level of the ocular surface from 4 to 9 points on the Oxford grading scale (15 points max)], subjective feeling of evaporative dry eye discomfort for more than 3 months [visual analogue scale (VAS) ≥ 2/10, ocular surface disease index (OSDI) ≥ 15], stable therapy (topical and systemic) ≥ 4 weeks,

and patients willing and being able to fulfill requirements of the trial protocol. Exclusion criteria included dry eye due to systemic disease, concomitant medication, malign conditions or idiopathic causes, history of ocular surgery during the past 3 months, malposition of the lids and/or lagophthalmos, punctum plugs during the past 3 months, contact lens wear, use of lipid containing eye drops during the past 3 months, use of other therapeutic ophthalmic drops during the past 3 months, sensitivity against any of the ingredients of the eye drops evaluated, pregnancy or breast feeding, woman with child bearing potential without regular and correct use of contraception, concomitant clinical trial participation within the last 4 weeks and inability to understand the written patient information.

Methods

All patients underwent 3 consecutive visits:

1. First examination (before initiating the treatment, D1), including the following tests and procedures: anamnesis, analysis of the subjective perception of dry eye-related disturbances (OSDI; Visual Analogue Scale (VAS) questionnaire), corrected distance visual acuity (CDVA), lipid layer thickness (LLT) measured with LipiView (TearScience, Johnson and Johnson Vision, Morrisville, USA) and KOWA DR-1 α (Kowa Company Ltd, Tokyo, Japan) devices, NIBUT measurement with the KOWA DR-1 α system, Goldman tonometry, and slit lamp assessment including analysis of lid margin (redness, manual expression of Meibomian glands, quality of Meibomian secretion), conjunctiva [conjunctival hyperemia level and lid-parallel conjunctival folds (LIPCOF)], and cornea (corneal staining with fluorescein). Slit lamp signs were graded using a scoring scale from 0 (absence) to 3 (maximum presence of the sign), except for corneal staining that was evaluated using the Oxford scale [10]. Specifically, with this scale, the cornea was divided into 5 sectors (central, superior, inferior, nasal, and temporal), each of which was scored on a scale of 0 - 3, where 0 means no staining and 3 means maximum staining, with a maximal score of 15 [10]. Patient discomfort and symptoms were evaluated using a VAS questionnaire, asking patients to score their DED in terms of frequency and severity of symptoms, feeling of eye pressure, burning, foreign body sensation, mucus formation, and itching. Once the patient's eligibility according to the inclusion and exclusion criteria was confirmed, the patient was randomized to one of the treatments with EvoTears®, Cationorm® MD sine or Systane® Balance. Patients were instructed to use their eye drops in accordance with the respective package insert (4 drops/day) and not less than two hours before the next follow-up examinations. No concomitant medications/treatments were allowed during the trial period.

2. Second examination (1 week after initiating the treatment, D7 ± 2 days), with OSDI analysis, VAS questionnaire, CDVA, thickness of the tear film lipid layer, NIBUT measurement, Goldman tonometry, and slit lamp assessment, including staining. The patients were asked about potential discomfort or problems with the treatment applied. In addition, the appearance of adverse events was also queried.

3. Third examination (1 month after initiating the treatment, D28 ± 2 days), including the same tests as in the 1-week exam. Likewise, the patient's subjective assessment of tolerability was reported as well as the physician's subjective assessment of treatment effectiveness and tolerability.

No application of any eye drops was allowed up to 2 hours before an examination.

Test medication

EvoTears® is an eye drop treatment for lipid deficient DED. The only ingredient is perfluorohexyloctane. This aliphatic, semifluorinated alkane is nonblurring and forms thin films together with lipids on ocular surface and thereby stabilizing the tear film. The molecule is chemically and physically inert and typically very well tolerated upon instillation in the eye. In contrast to aqueous eye drops, no additives such as preservatives, emulsifiers or phosphates are contained. The average drop size of EvoTears® is about 1/3 the drop size of aqueous eye drops (approximately 10 µl) [7].

Cationorm® MD sine is a moisturizing, lipid-containing medical device consisting of a cationic oil-in-water emulsion. It is an aqueous solution containing small positively charged oily core droplets. It is used for the symptomatic treatment of dry eyes. The mode of action is based on the electrostatic attraction between the positively charged particles of the emulsion and the negatively charged ocular surface (cornea, conjunctiva) [11].

Systane® Balance is a moisturizing, lipid-containing medical device, containing propylene glycol, HP guar and LipiTech™ (paraffin oil). It is used for the treatment of symptomatic dry eyes. The lipid-containing supplements are aimed to stabilize the disturbed lipid layer of the tear film [12].

Dosing was 4 x 1 drop per day for all tested medication. Deviations from this schedule were documented.

Statistical analysis

For sample size calculation, peer review publications were used to define means and standard deviations associated to NIBUT values [10,13]. Sample size calculation was carried out according to the Dupont & Plummer guidelines using the Power and Sample Size software version 3.1.2 (Free access at http://biostat.mc.vanderbilt.edu/PowerSampleSize) [14]. Ten patients per group were found as necessary to detect a difference in NIBUT increase (baseline vs. 1 month) of 2.1 s between EvoTears® and Systane® Balance or between EvoTears® and Cationorm® MD sine, with a given standard deviation of 1.5, a statistical power of 85%, and a significance level of 0.05. It was planned to recruit a total of 40 patients to compensate for possible dropouts.

Data analysis was performed using STATA 13.1 software (Stata Corp, College Station, Texas USA). Continuous data are presented as mean and standard deviation or median and range, whereas categorical data are expressed as percentages and absolute values. Repeated-measures ANOVA (including post-hoc Tukey test) was computed to compare the 3 trial groups over time. For accurate statistical analysis of the visual acuity outcomes, decimal values were transformed into logMAR notation. For all monocular variables, only 1 eye per patient was included in the data analysis. Specifically, the eye of the patient with the lower NIBUT value at day 1 was selected for analysis. If a patient had the same NIBUT value in both eyes, the left eye was selected. Furthermore, Fisher's exact test was used to compare subjective assessment of tolerability and effectiveness among groups. For all statistical tests, a p-value of less than 0.05 was considered as statistically significant.

Results

Patient demographics and baseline data are summarized in table 1. As shown, no statistically significant differences in baseline parameters between groups were detected ($p > 0.05$). With the exception of one patient, all subjects adhered to the treatment schedule of 4 x 1 drop per day. One patient used up to 8 drops per day, which was reported at the 1-week follow-up.

	Total	EvoTears	Cationorm	Systane	p-value
Patients/eyes (n)	30/30	10/10	10/10	10/10	
Gender	15 M/15 F	6 F/4 M	5 F/5 M	4 F/6 M	0.897
	50%/50%	60%/40%	50%/50%	40%/60%	
Age (y)	55.03 (18.63) 58.5 (23 to 92)	61.9 (17.08) 63.5 (30 to 92)	52.2 (19.27) 55.5 (24 to 79)	51.0 (20.35) 54.0 (23 to 74)	0.383
Height (cm)	169.4 (8.93)	167.3 (11.04)	170.2 (8.2)	170.7 (7.79)	0.671
	168 (156 to 194)	167 (156 to 194)	171 (159 to 183)	170 (158 to 182)	

Weight (kg)	73.3 (14.9)	72.3 (17.0)	81.6 (12.9)	65.9 (11.0)	0.054
	70 (45 to 105)	68.5 (45 to 102)	80.5 (60 to 105)	62 (52 to 88)	
Visual Acuity (logMar)	0.09 (0.14)	0.12 (0.21)	0.02 (0.04)	0.12 (0.12)	0.201
	0.05 (0 to 0.70)	0.10 (0 to 0.70)	0 (0 to 0.10)	0.10 (0 to 0.30)	
NIBUT	6.17 (1.21)	6.10 (1.29)	6.10 (1.20)	6.3 (1.25)	0.918
	6 (4 to 9)	6.5 (4 to 8)	6.0 (4 to 8)	6 (5 to 9)	
OSDI	42.3 (18.6)	47.7 (19.5)	44.8 (14.2)	34.5 (20.5)	0.260
	39.2 (16.6 to 97.9)	40.6 (31.2 to 97.9)	51 (18.7 to 60.4)	29.1 (16.6 to 87.5)	
Lipid layer thickness (LipiView)	69.6 (20.1)	76.1 (21.7)	73.4 (18)	59.3 (18)	0.132
	63 (40 to 100)	69.5 (47 to 100)	75 (40 to 100)	52 (40 to 99)	
Lipid layer thickness (KOWA)	2.91 (0.68)	3.28 (0.71)	2.90 (0.62)	2.56 (0.58)	0.075
	3.0 (2 to 4.5)	3 (2.5 to 4.5)	2.75 (2 to 4)	2.5 (2 to 3.5)	

Table 1: *Patient demographics and baseline data in the 3 study groups; values presented as mean (standard deviation), median (range).*

Abbreviations: NIBUT: Non-Invasive Break-Up Time; OSDI: Ocular Surface Disease Index

NIBUT changes

NIBUT on D1 (baseline) was below 7s in all groups (Figure 1): 6.1 ± 1.3 for EvoTears®, 6.1 ± 1.2 for Cationorm® MD sine and 6.3 ± 1.3s for Systane® Balance. Local treatment led to a significant increase of NIBUT values from below 7s to more than 10 s at both D7 and D28 in all 3 groups compared to D1 ($p < 0.001$) (Figure 1). Differences between groups in NIBUT during the follow-up did not reach statistical significance ($p > 0.05$), although there was a larger absolute and percentual increase in NIBUT at D28 vs D1 (+121.3%) in the EvoTears® group (Table 2). Likewise, there were no significant differences in NIBUT between D7 and D28 in all groups ($p = 0.231$).

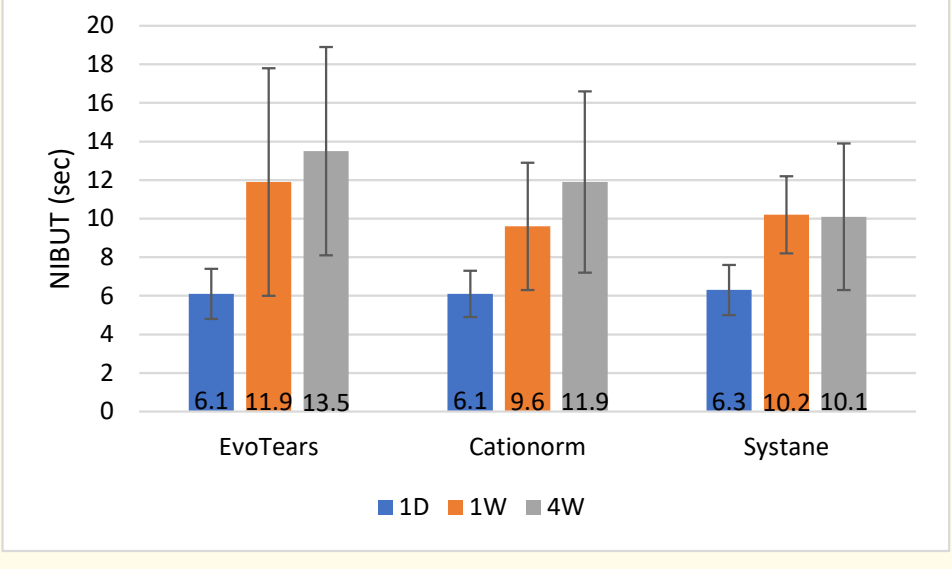

Figure 1: *Changes in NIBUT in the 3 groups during the follow-up (means ± standard deviation).*

	NIBUT change in % vs D1	
	D7	D28
EvoTears	+95.1%	+121.3%
Cationorm	+57.4%	+95.1%
Systane	+63.9%	+62.3%

Table 2: *NIBUT percentual change in the 3 groups during the follow-up. Abbreviations: NIBUT: Non-Invasive Break-Up Time; D: Day.*

Slitlamp examination

In all groups, expression of Meibomian glands decreased at D7 and D28 when compared to baseline ($p < 0.001$), with no significant changes between D7 and D28 ($p = 0.722$, Figure 2). No statistically significant differences were found between groups in the manual expression of the Meibomian glands ($p = 0.363$). The quality score of Meibomian secretion changed significantly from 1.8 ± 1.0 on D1 to 0.1 ± 0.3 on D28 in in the EvoTears® group, from 0.7 ± 0.5 on D1 to 0.2 ± 0.4 on D28 in the Cationorm® MD sine group, and from 0.8 ± 0.4 on D1 to 0.1 ± 0.3 on D28 in the Systane® Balance group ($p < 0.001$, Figure 2).

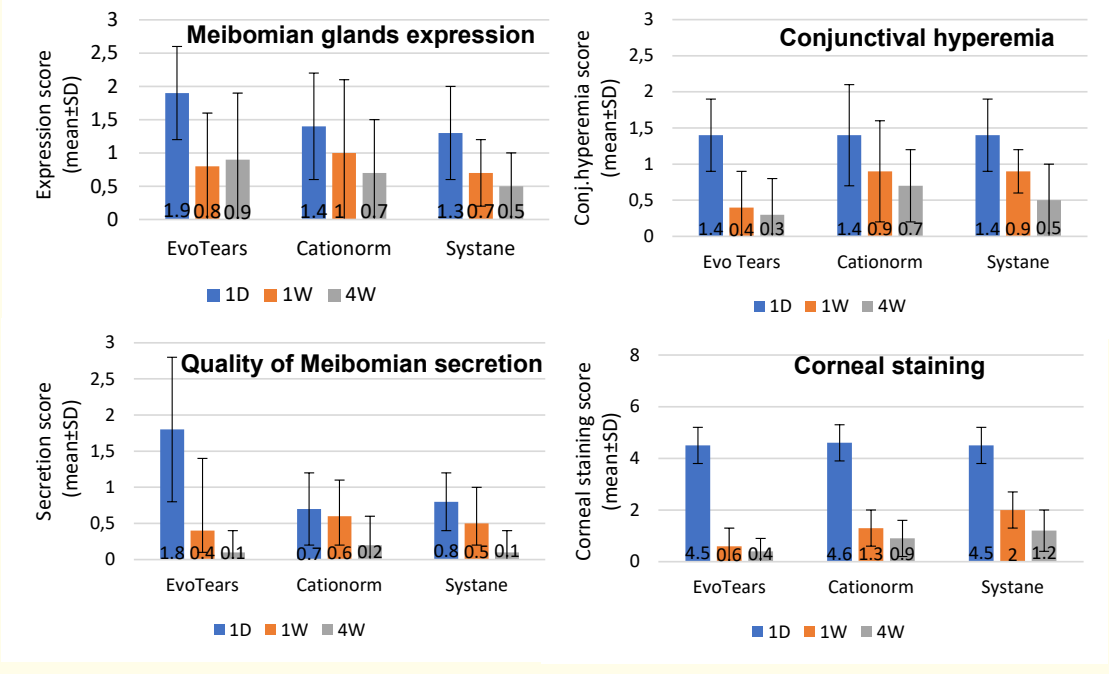

Figure 2: *Changes in the evaluation of different slit lamp signs in the 3 groups, including expression of Meibomian glands (score, 0 to 3), quality of Meibomian secretion (score, 0 to 3), conjunctival hyperemia (score, 0 to 3), and corneal staining (score, 0 to 15) (means ± standard deviation).*

In all groups, the level of conjunctival hyperemia decreased significantly during treatment ($p < 0.001$, Figure 2). In contrast, no significant changes were found in LIPCOF scores in any of the 3 groups during the follow-up ($p > 0.05$), although there was a tendency for a lowering of LIPCOF from D1 to D7.

Corneal staining with fluorescein decreased significantly in all treatment groups over time ($p < 0.001$, Figure 2). Staining decreased between 1 day and 1 week from 4.5 ± 0.7 to 0.6 ± 0.7, from 4.6 ± 0.7 to 1.3 ± 0.7 and from 4.5 ± 0.7 to 2.0 ± 0.7 in the EvoTears®, Cationorm® and Systane® group, respectively. At D7, patients with EvoTears® treatment showed a lower corneal staining than patients with Systane® Balance treatment ($p = 0.007$). There were no significant differences in corneal staining between D7 and D28 for any of the 3 treatments.

Other clinical changes

In all groups, a significant decrease of OSDI over time was observed. For all treatments, a statistically significant improvement in OSDI was observed at D7 and D28 compared to baseline ($p = 0.008$ and $p = 0.001$, respectively). Changes from D7 to D28 did not reach statistical significance ($p = 0.808$) in any of the groups. No statistically significant differences in OSDI were found between the groups ($p = 0.135$), with all groups showing the same trend over time. Systane® Balance treatment showed a lower OSDI score than EvoTears® and Cationorm® MD sine treatment in absolute terms over the follow-up period, but this difference was not statistically significant ($p > 0.05$). Some non-statistically significant trends were observed in each of the three groups analyzed, including a trend to a more pronounced improvement by EvoTears® treatment on D28 (-30%) in patients with baseline "severe" OSDI, lower improvement in OSDI on D7 (-10%) and D 28 (-20%) with Cationorm® MD sine treatment and a deterioration of OSDI from D7 (-20%) to D28 (-10%) with Systane® Balance treatment.

LLT measured with LipiView was not significantly different between groups at each follow-up visit ($p = 0.534$). When performing an analysis by group, EvoTears® treatment was found to induce a significant decrease in LLT at D28 when compared to baseline ($p = 0.009$), whereas Cationorm® MD sine and Systane® Balance treatments did not induce significant changes in LLT ($p > 0.05$). Figure 3 displays LLT changes measured with the KOWA device in the three groups. No statistically significant differences in LLT KOWA scores among treatment groups were found ($p = 0.334$). There was a tendency towards a slight non-significant decrease of the LLT over time in patients receiving EvoTears® and Cationorm® MD sine eye drops, which was not seen in the Systane® Balance group on D28 compared to baseline ($p = 0.054$).

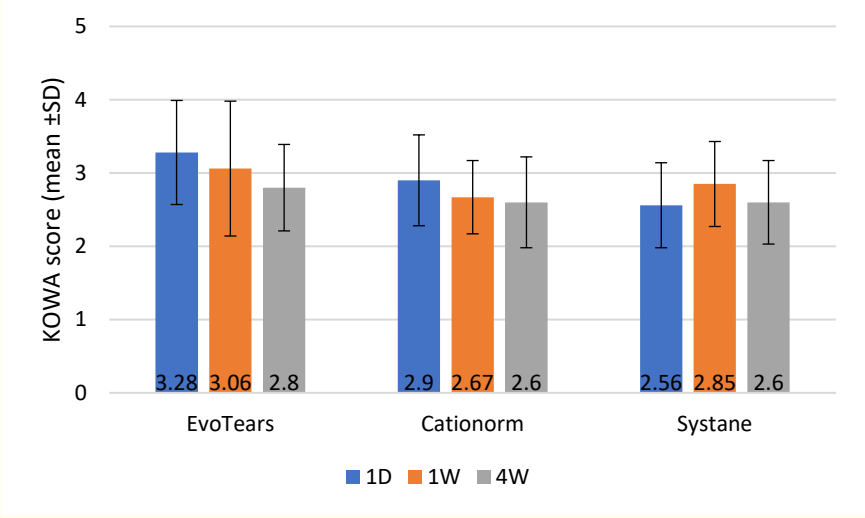

Figure 3: *Changes in the measurement of lipid layer thickness using the KOWA device (KOWA scoring system) in the 3 groups during the follow-up (means ± standard deviation).*

Table 3 displays the visual acuity and intraocular pressure (IOP) data during the follow-up in the 3 groups. No statistically significant differences in visual acuity were found among the 3 groups (p = 0.413), as well as no significant visual changes over time (p = 0.463). Likewise, the intraocular pressure (IOP) remained stable across visits. There was no statistical difference in IOP among the three groups (p > 0.05). Mean baseline IOPs were close to 14 mmHg and did only slightly change during the follow-up period (p > 0.05, see table 3).

		Visual Acuity (logMAR)			IOP (mmHg)		
		D1	D7	D28	D1	D7	D28
EvoTears	Mean	0.12	0.07	0.21	13.9	13.3	14.2
	SD	0.21	0.16	0.40	1.0	1.3	1.2
Cationorm	Mean	0.02	0.09	0.04	14.3	14.0	14.4
	SD	0.04	0.13	0.05	1.3	1.6	1.6
Systane	Mean	0.12	0.08	0.11	13.8	13.8	14.5
	SD	0.12	0.12	0.13	1.1	1.3	1.0
All	Mean	0.09	0.08	0.12	14.0	13.7	14.4
	SD	0.14	0.14	0.25	1.1	1.4	1.2

Table 3: *Visual acuity data and intraocular pressure development in the 3 groups during the follow-up. Abbreviations: SD: Standard Deviation; IOP: Intraocular Pressure; D: Day.*

Subjective patient and physician assessment

The VAS questionnaire showed a statistically significant improvement in the frequency of symptoms at 1 week and 1 month for each group, when compared to the baseline visit (p < 0.001, table 4).

		Patient questionnaire VAS			
		D1	D7	D28	p-value
Frequency of symptoms	EvoTears	6.7 ± 0.66	3.99 ± 0.66	3.19 ± 0.66	0.446
			-40.4%	-52.4%	
	Cationorm	7.25 ± 0.62	5.81 ± 0.62	3.65 ± 0.62	
			-19.9%	-49.7%	
	Systane	6.4 ± 0.7	4.19 ± 0.7	3.14 ± 0.7	
			-34.5%	-50.9%	
Severity of symptoms	EvoTears	6.48 ± 0.52	3.87 ± 0.52	2.55 ± 0.52	0.239
			-40.3%	-60.6%	
	Cationorm	6.85 ± 0.49	5.68 ± 0.49	3.81 ± 0.49	
			-17.1%	-44.4%	
	Systane	6.52 ± 0.53	3.77 ± 0.56	2.73 ± 0.56	
			-42.2%	-58.1%	
Lacrimation	EvoTears	4.21 ± 0.37	3.25 ± 0.37	2.71 ± 0.37	0.888
			-22.8%	-35.6%	
	Cationorm	4.05 ± 0.37	3.62 ± 0.37	2.74 ± 0.37	
			-10.6%	-32.3%	
	Systane	4.65 ± 0.37	3.66 ± 0.37	3.4 ± 0.37	
			-21.3%	-26.9%	

Feeling of eye pressure	EvoTears	5.1 ± 0.53	3.05 ± 0.53	2.11 ± 0.53	0.719
			-40.2%	-58.6%	
	Cationorm	5.85 ± 0.53	4.05 ± 0.53	2.13 ± 0.53	
			-30.8%	-63.6%	
	Systane	5.2 ± 0.53	3.93 ± 0.53	2.84 ± 0.53	
			-24.4%	-45.4%	
Burning	EvoTears	6.04 ± 0.57	3.32 ± 0.57	2.63 ± 0.57	0.325
			-45.0%	-56.5%	
	Cationorm	6.85 ± 0.57	5.59 ± 0.57	3.39 ± 0.57	
			-18.4%	-50.5%	
	Systane	5.8 ± 0.57	4.63 ± 0.57	2.9 ± 0.57	
			-20.2%	-50.0%	
Foreign Body Sensation	EvoTears	6.13 ± 0.73	4.72 ± 0.73	4.19 ± 0.73	0.400
			-23.0%	-31.6%	
	Cationorm	6.9 ± 0.73	5.98 ± 0.73	3.92 ± 0.73	
			-13.3%	-43.2%	
	Systane	4.91 ± 0.73	3.5 ± 0.73	2.84 ± 0.73	
			-28.7%	-42.2%	
Mucus formation	EvoTears	2.55 ± 0.37	1.96 ± 0.39	1.07 ± 0.39	0.997
			-23.1%	-58.0%	
	Cationorm	2.5 ± 0.37	2.13 ± 0.37	0.79 ± 0.37	
			-14.8%	-68.4%	
	Systane	2.0 ± 0.37	1.66 ± 0.37	1.5 ± 0.37	
			-17.0%	-25.0%	
Itching	EvoTears	5.76 ± 0.44	3.77 ± 0.44	2.54 ± 0.44	0.043
			-34.5%	-55.9%	
	Cationorm	4.95 ± 0.44	3.52 ± 0.44	2.44 ± 0.44	
			-28.9%	-50.7%	
	Systane	1.85 ± 0.44	1.3 ± 0.44	0.91 ± 0.44	
			-29.7%	-50.8%	

Table 4: *Evaluation of the patients' symptoms using the VAS questionnaire in the 3 groups; % improvement from baseline; data shown as mean ± standard deviation; P values report significance between treatments. Abbreviation: D: Day.*

Moreover, there was an additional significant improvement of subjective symptoms between 1 week and 1 month (p = 0.028). Specifically, the frequency of symptoms decreased in each group by approximately 50% from D1 to D28. Severity improved by 60.6% in the EvoTears® group, 44.4% in the Cationorm® MD sine group and 58.1% in the Systane® Balance group (Figure 4). Concerning the assessment of treatment tolerability, no statistically significant differences were found between groups (p > 0.05). For EvoTears®, 90% of patients assessed tolerability as good or very good and the physician's assessment of tolerability and efficacy was good or very good in 90%

and 100% of cases, respectively. Systane® Balance and Cationorm® MD sine eye drops were assessed by the physician and the patients as good or very good in each item in 100% of the cases.

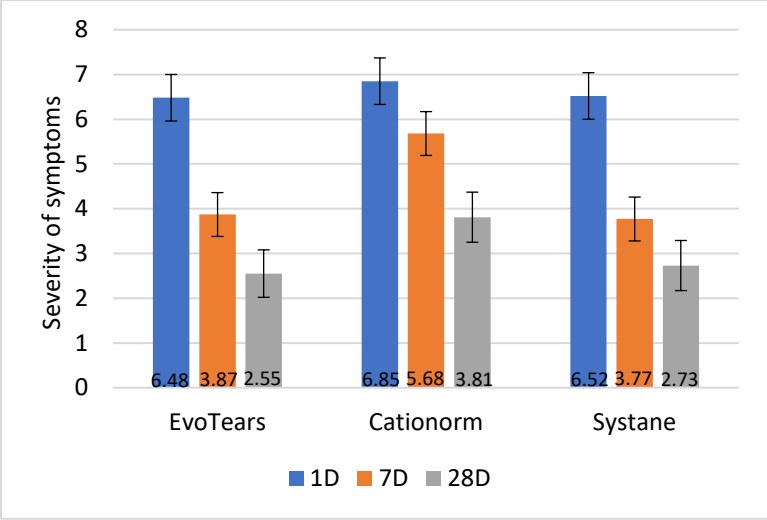

Figure 4: *Changes in the scoring (0, best to 10, worst) for the severity of symptoms evaluated with the VAS questionnaire in the 3 groups during the follow-up (means ± standard deviation).*

Safety outcomes

No adverse events, serious adverse events or dropouts due to treatment medications were noted in any group during the trial period.

Discussion

In the current study, a comparative analysis of the clinical outcomes obtained with water-free eye drops containing perfluorohexyloctane as only ingredient and two different eye drops containing lipid, water and polymers has been performed. To our knowledge, this is the first study comparing eye drops containing perfluorohexyloctane with other types of aqueous eye drops in eyes with evaporative DED and mild to moderate MGD. It should be considered that an untreated lipid deficiency leads to tear film instability and increased evaporation, which affects the integrity and functionality of corneal and conjunctival cells [15].

The clinical outcome was evaluated in terms of changes in NIBUT, tear film LLT, subjective symptoms, slit lamp examinations and a subjective assessment of the efficacy and tolerability by the physician and the patients. For the LLT measurement, two different validated interferometric devices have been used, Lipiview [16] and KOWA DR-1 α [17].

NIBUT as a measure of tear film stability increased significantly during the follow-up period with all tested products. Differences between the three treatment options were not statistically significant but showing a trend that perfluorohexyloctane is more effective compared to the other two lipid-containing aqueous eye drops. An increase in NIBUT after 4 or 6 weeks of treatment with the watery lipid-containing eye drops Cationorm® MD sine and Systane® Balance has been also reported in previous studies [11,18]. Concerning EvoTears®, Steven., *et al*. demonstrated in a prospective, multicentered, observational 6-week clinical trial that a 4-times daily application of EvoTears® significantly increased TBUT in patients with hyperevaporative DED from approximately 6 s to approximately 9 s. These

authors also reported a concomitant improvement in OSDI [8]. In the current study, a significant improvement/decrease of OSDI over time was observed with all 3 treatments, with a non-significant trend to a more pronounced improvement with EvoTears® in patients with baseline "severe" OSDI. Specifically, the OSDI classification score "severe" decreased after treatment with perfluorohexyloctane eye drops by 30% on D7 and on D28.

Changes in LLT measured with Lipiview were detected in the EvoTears® group, with a significant decrease at the end of the follow-up when compared to baseline. In contrast, significant modifications in LLT were not detected with the other two types of eye drops. When LLT measurements were performed with the KOWA system, no significant changes were observed, with only a tendency towards a slight decrease of LLT score over time in patients receiving EvoTears® and Cationorm® MD sine eye drops. These outcomes are not consistent with those reported by Schmidl., *et al*. who found by OCT measurements that perfluorohexyloctane eye drops increased LLT over time, which was associated to a stabilization of the lipid layer [19]. Considering that different methods of measurement can lead to completely different results in the same eye and that LLT does not necessarily correlate with tear film evaporation may start a discussion whether the thickness of the lipid layer correlates with the rate of evaporation of tears [20,21]. Several studies showed that NIBUT, which is a parameter used to evaluate the tear film stability, is not significantly correlated with LLT [15,20,22-24]. This is also consistent with the findings obtained by Arita., *et al*. confirming that an increase in LLT does not necessarily improve tear film stability [25]. Furthermore, no clear and consistent changes have been observed in LLT after the use of different types of eye lubricants [26]. EvoTears® showed an increased NIBUT and a lower LLT which was an unexpected result. The tear film showed a very homogeneous color and distribution. Therefore, it might be discussed that a thin but elastic and evenly distributed lipid layer should be achieved to reduce tear evaporation. More research is needed to define the real clinical relevance of the measurement of LLT and its role on the evaluation of DED treatments.

Besides the improvement in NIBUT with the three treatment options, an improvement in the expression of Meibomian glands, an improvement of quality of Meibomian secretion and a decrease in the level of conjunctival hyperemia and corneal staining was observed. This improvement of fluorescein-positive lesions of cornea and conjunctiva has been also reported for each type of treatment separately [9,11,26], as well as a decrease of the manually expressed content of Meibomian glands [27]. Stagnant secretions with poor quality that block the gland opening thus were reduced by this lipid layer substitution treatment. With the use of EvoTears®, the most pronounced improvement in the quality of Meibomian secretion was observed, suggesting a sustained effect on Meibomian glands as demonstrated in previous research [7]. All these improvements with the three eye drops contribute to the amelioration of DED symptoms evaluated with the VAS questionnaire, with improvements at the end of the follow-up in 90% to 100% of cases. Accordingly, the patients and the investigator assessed the efficacy and tolerability as acceptable or very good.

Finally, it should be acknowledged the potential limitations of this study. The open-label character is a clear limitation of the study and the small number of cases with which only limited statements can be made about parameters for which no power was applied. Therefore, differences between the groups should be confirmed in future comparative clinical trials.

Conclusion

The efficacy and safety of EvoTears® are comparable to the two aqueous lipid-containing eye drops for the treatment of DED combined with mild to moderate MGD. With these eye drops, 28 days of treatment were sufficient to improve signs and symptoms. Furthermore, the clinical effect of water-free EvoTears® in this study shows a trend to a more beneficial effect compared to lipid containing aqueous eye drops. Comparative studies with a larger sample size might help to elaborate differences of the investigated parameters between the treatment options.

Disclosure

This study has been sponsored by URSAPHARM Arzneimittel GmbH. Dorothea Groß is employee of URSAPHARM. The authors report no other conflicts of interest in this work.

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