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ORIGINAL RESEARCH

Efficacy of two-month treatment with Xiloial® eyedrops for discomfort from disposable soft contact lenses

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Purpose: To evaluate the efficacy and tolerability of Xiloial® monodose eyedrops in the treatment of patients suffering from subjective symptoms of discomfort related to disposable soft contact lens (dSCL) wear.

Methods: Fifteen (12 female, three male, medium age 39 ± 9 years) dSCL wearers were enrolled. Inclusion criteria were Ocular Surface Disease Index (ODSI) symptom questionnaire score >12, tear film break-up time (TFBUT) <10 sec, Schirmer test I >10 mm over five minutes, mild punctuate keratopathy, and conjunctival staining (Oxford grading ≤4). Monodose Xiloial eyedrops were administered three times daily for a two-month period. Patients were evaluated at enrollment, after three days of washout (baseline), and after one and two months of treatment, by OSDI score, Schirmer test I, TFBUT, ferning test, ocular surface damage (Oxford grade), and serum albumin in tears (index of passive exudation related to serum leakage).

Results: At endpoint versus baseline, respectively, the mean ± standard deviation of all variables improved as follows: OSDI (8.5 ± 3 versus 20.2 ± 1.6); TFBUT (9.6 ± 1.1 versus 7.1 ± 1.0); Oxford grading (0.5 ± 0.1 versus 3.6 ± 0.8); ferning test (2 ± 1 versus 2.4 ± 0.5); and Schirmer test I (14.6 ± 1.1 versus 12 ± 2.1), with $P < 0.05$ for all variables (Friedman and Wilcoxon tests). Tolerability was high, with no adverse events noted.

Conclusions: A two-month treatment with Xiloial showed good tolerance and appeared to reduce ocular surface damage and symptoms of discomfort.

Keywords: discomfort, dry eye, disposable contact lens, biopolymer tamarind seed polysaccharide–hyaluronic acid

Introduction

Symptoms of ocular surface discomfort are common in contact lens wearers, affecting about half of them.[1,2] As many as 20% of contact lens wearers experience symptoms that are severe enough to reduce their wearing time.[3,4] Furthermore, 12%–24% of contact lens patients discontinue contact lens wear permanently.[4,5] The most common reason for lens discontinuation is discomfort, affecting about 49%–72% of wearers.[5–7] Other symptoms frequently affecting lens wearers are dryness, itchiness, grittiness, photophobia, soreness, and pain.[4] In spite of this, 65% of contact lens wearers think that this is the ideal form of visual correction.[4] The speculated mechanism of contact lens-related discomfort and dryness is multifactorial, including evaporation,[8] hypoesthesia,[9] decreased tear production with concurrent increased osmolarity,[10] and inflammation.[11–13]

Tear film is critical to successful wearing of contact lenses. A stable tear film is important to promote clear vision and to reduce optical aberration created by tear film breakup.[14]

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Instillation of tear substitutes may improve the optical quality of vision in contact lens-related dry eye syndrome,[15,16] and preservative-free tear substitute formulations are preferable because of the toxicity of preservatives.[17]

Evolving concepts in tear substitute formulation suggest that better compliance can be achieved by improving the stability of the tear film/corneal epithelium interface with mucoadhesive properties and enhanced retention time on the surface.[17] In addition, a hypotonic substitute can lower tear hyperosmolarity, a common feature in any type of dry eye-related disease.[18]

The present study evaluated the efficacy and tolerability of a two-month treatment in symptomatic disposable soft contact lens wearers with an innovative preservative-free hypo-osmolar copolymer already commercially available in Italy (Xiloial® eyedrops; Farmigea, Pisa, Italy), formulated to strengthen the synergistic properties of hyaluronic acid and tamarind seed polysaccharide (TSP).

Methods

Study population

Fifteen disposable contact lens wearers (12 women aged 40 ± 9 years, three men aged 37 ± 9 years) were enrolled at one research site in Bologna, Italy. Patients were full-time contact lens wearers, and brand and material of contact lens type, replacement schedule, and solutions used are reported in Table 1. The study was approved by the Independent Ethics Committee and conducted in accordance with the ethical principles of the Declaration of Helsinki and the current legislation on clinical research in Italy. All subjects signed an informed consent form before starting the study.

Materials

Sterile saline (0.9% NaCl; Mini-Plasco, B. Braun, Meisungen, Germany) was used for the washout period. Monodose Xiloial eyedrops (hyaluronic acid 0.2% and 0.2% TSP, 280 mosm/L, pH 7.4) was used as the test solution.

Study design

This was a prospective, open-label, single-center study to investigate the effect of Xiloial treatment on discomfort in disposable contact lens wearers without suspending lens wear during the treatment period. The study included four visits during two months, ie, visit 0 (V0, screening), visit 1 (V1, day 0/baseline, made 1–3 days after V0), visit 2 (V2, made 30 days after V1), visit 3 (V3, endpoint, 60 days after V1) .

Inclusion and exclusion criteria

Patients older than 18 years, with a score >12 on the Ocular Surface Disease Index (OSDI) symptom questionnaire,[19] tear film break-up time (TFBUT) lower than 10 seconds, and Schirmer test I >10 mm in five minutes were enrolled. Patients with punctuate keratopathy >1 by Oxford grading[20] were excluded, as well as pregnant women, and people with concurrent ocular surface pathologies, eye surgery in the last six months, concomitant ocular treatment, (except for tear substitutes), or known to be allergic to any of the components of Xiloial (Table 2).

Table 1 Contact lens types (brand and material), replacement schedule, solutions, wear length (years and daily) are listed for each enrolled patient

Patient	Wear/day (hours)	Wear/total (years)	Material	Replacement schedule	Contact lens solution	Past intolerance
1	10	5	Iotrafilcon A	1 day	none	yes
2	10	8	Etafilcon A	15 days	Opti-Free	no
3	10	5	Etafilcon A	1 day	none	yes
4	10	5	Omafilcon A	1 day	none	yes
5	10	5	Etafilcon A	1 day	none	yes
6	8	1	Hilafilcon B	1 day	none	no
7	10	5	Nelfilcon A	1 day	none	yes
8	10	8	Polymacon	15 days	ReNu MultiPlus	no
9	10	8	Galifilcon A	7 days	AOSept	no
10	12	10	Iotrafilcon A	1 day	none	yes
11	12	12	Hilafilcon B	1 day	none	yes
12	12	10	Etafilcon A	15 days	Opti-Free	no
13	8	5	Polymacon	15 days	ReNu MultiPlus	no
14	8	12	Etafilcon A	15 days	AOSept	no
15	12	12	Polymacon	15 days	ReNu MultiPlus	no
Mean ± SD	10.1 ± 1.4	7.6 ± 2.8				

Abbreviation: SD, standard deviation.

Procedure

At the screening visit, subjects' demographic information was recorded, along with current/prior use of medications, tear substitutes, and ocular pathologies. Subjects who met the inclusion criteria signed the informed consent and were enrolled. They were then given saline solution as a washout to minimize any effect from previous medication use. Subjects were instructed to use the saline drops three times daily in both eyes, and to refrain from administering any other tear drops after 8.00 am on the day of their next visit.

After 1–3 days, subjects returned (V1) for eligibility follow-up examination, at which the TFBUT, Schirmer test I, and OSDI questionnaire were repeated. In addition, the ferning test and measurement of exudated serum albumin in tears were carried out. Subjects who remained eligible for the study were dispensed Xiloial monodose eyedrops and were instructed to use one drop in each eye (upon awakening without contact lenses in, early afternoon with contact lenses in, and before bedtime without contact lenses in).

After 30 (± 2) days (V2), subjects returned for follow-up. The same examination measurements and questions were repeated as for V0, except for the ferning test and serum albumin measurement. Tolerability was assessed by visual analog scale scoring of specific symptoms (blurring, redness, itching, stinging after instillation) and any adverse events were recorded.

The same examination as for V0 was then repeated after a further 30 (± 2) days (V3), which represented the endpoint of the study.

Office visits were performed after contact lens removal, and the conditions were the same for all visits in that they were done at approximately the same time of day (in the early afternoon), and in a dim-lit room controlled for temperature and humidity. A slit-lamp biomicroscope examination was conducted at all visits by two independent examiners (VP and NB) to record any abnormalities in the conjunctiva, lids/eyelashes, anterior chamber, iris, and lens.

TFBUT was measured and recorded (average of three measurements) using 5 µL sodium fluorescein (Fluoralfa 0.25%; Alfa Intes, Casoria, Italy). Schirmer test I was performed by using validated sterile test strips (ContaCare Ophthalmics and Diagnostics, Gujarat, India), as described elsewhere.[21] To quantify corneal and conjunctival surface damage, fluorescein sodium staining was graded against standard charts according to the Oxford grading system,[20] with the aid of a yellow Kodak Wratten 12 barrier filter. The ferning test was performed as previously described[22] at baseline and at endpoint. The patterns of arborisation (ferning) from a drop of tear collected from the lower meniscus and allowed to dry by evaporation were classified as Types I–IV (Type I, uniform arborisation; Type II, empty spaces begin to appear among ferns; Type III, single ferns are small, incomplete with rare or no branching; Type IV, no ferns), where Types I and II are reported to be normal, and Types III and IV are reported to be abnormal.[22]

Exudated serum albumin was measured at baseline and endpoint in tear samples using a commercial enzyme-linked immunosorbent assay kit (Bio-Rad, Hercules, CA) according to the manufacturer's instructions, and 10 µL unstimulated tears were collected from each subject using a laboratory micropipette (Pipetman®; Gilson Intl BV, The Hague, The Netherlands) with a sterile disposable tip.

Statistical analysis

We collected data for the more uncomfortable eye, or arbitrarily from the right eye in case of equivalence. Data were statistically analyzed using SPSS 9.0 (SPSS Inc., Chicago, IL) and MedCalc 5.0 (MedCalc Software, Mariakerke, Belgium) software. The Wilcoxon matched-pairs test was applied for ferning and albumin data, while the nonparametric paired Friedman test was used to evaluate all other variables. Values for $P \leq 0.05$ were regarded as statistically significant. Descriptive statistics were performed for all variables, ie, mean and standard deviation (SD). Spearman's correlation analysis was applied to verify the relationship between variables and data from the worn contact lens regimen, its duration, and any history of intolerance.

Results

All subjects successfully completed the study. Data are summarized in Table 3 and graphed in Figure 1a–f. No significant changes in any of the tests applied were observed between screening and baseline visits.

Symptoms of ocular discomfort

A progressive and significant lowering of discomfort symptoms was found after one month of treatment. At the endpoint, OSDI score was reduced to more than half that recorded at baseline (Table 3, Figure 1a). All patients homogeneously displayed the same trend, and no correlation was found between the time of symptom recovery and any contact lens wear parameter.

Tear film break-up time

A significant increase in TFBUT was found after one month of treatment, which increased even further at the endpoint visit, matching the results versus baseline (Table 3,

Table 2 Methods and tests utilized in the study, listed in sequence of performance

Test sequence	Basis	Values to be recorded	Pathologic values
1. OSDI questionnaire	Subjective symptoms	score 1–100	>12[19]
2. Schirmer test I	Indirect measure of total tear secretion	mm wetting in five minutes	≤5 mm/5 min[21]
3. Ferning test	An index of tear stability	Grade I/IV	≥Grade II/III[22]
4. Tear collection for albumin dosage	An index of blood barrier breakdown and passive exudation	mg/mL	≥0.130 mg/mL[31]
5. TFBUT	An index of tear film stability	Seconds	≤10 sec[21]
6. Oxford grading	An index of ocular surface damage	Grade 0–3 for six areas	≥9/18[20]

Abbreviations: OSDI, Ocular Surface Disease Index; TFBUT, tear film break-up time.

Figure 1b). A progressive increase in TFBUT values was recorded in all patients in both eyes.

Ocular surface damage

Ocular surface epithelial damage (by Oxford grading score) was significantly reduced in six of 15 patients after one month of treatment. The damage score disappeared at the endpoint of two months' treatment in eight of 15 patients, despite ongoing contact lens wear (Table 3, Figure 1c). Very mild conjunctival staining residues (score 1 or 2) were found in the remaining seven patients at the endpoint. The timing of recovery from damage did not appear to be related to any contact lens wear parameters.

Ferning test

Ferning grade was reduced in eight subjects and unchanged in seven subjects after two months of treatment. Statistical analysis demonstrated a significant ($P = 0.03$) reduction of values at endpoint versus baseline (Table 3, Figure 1d).

Schirmer value

Four patients did not show any change in the Schirmer value, while a mild increase was observed in the remaining 11 patients. The Schirmer value significantly increased at the endpoint and was evident only after two months of treatment (Table 3, Figure 1e).

Albumin in tears

Inhomogeneous results were obtained for exudated serum albumin in tears. Analyzing the data as a whole, no statistically significant difference was demonstrated at the endpoint versus baseline (Table 3, Figure 1f). Only the subgroup of patients who had not experienced any contact lens wear intolerance in the past showed a statistically significant decrease in exudated serum albumin at the endpoint versus baseline (0.359 ± 0.04 versus 0.388 ± 0.03, $P = 0.007$, Wilcoxon test) but no correlation was found with other contact lens wear characteristics.

Tolerability

The visual analog scale tolerability questionnaire showed a very good response to treatment. No blurred vision, ocular redness, burning, or itching were reported, nor any adverse events.

Discussion

Xiloial is a new ophthalmic preparation based upon the unique synergistic action of TSP and high molecular weight hyaluronic acid obtained by biotechnologic synthesis.

TSP is a neutral polymer showing a branched-chain structure similar to that of corneal and conjunctival mucus transmembrane proteins, specifically MUC1. This particular structure accounts for distinctive mucomimetic, mucoadhesive, and pseudoplastic properties[23,24] which render

Table 3 Summary of study results

Parameter*	Screening visit	Baseline	30 days	60 days	Level of significance $P < 0.05$
OSDI	20.20 ± 1.66	20.20 ± 1.78	14.40 ± 2.97	8.5 ± 3.00	$P < 0.05$ (Friedman test)
TFBUT	7.07 ± 1.03	7.07 ± 0.80	8.20 ± 0.77	9.60 ± 1.12	$P < 0.05$ (Friedman test)
Oxford grading	3.67 ± 0.82	3.67 ± 0.82	2.07 ± 0.96	0.53 ± 0.64	$P < 0.05$ (Friedman test)
Ferning test	–	2.4 ± 0.47	–	2.03 ± 0.13	$P < 0.05$ (Wilcoxon test)
Schirmer test I	12 ± 2.10	13 ± 2.36	13.93 ± 1.91	14.60 ± 1.06	$P < 0.05$ (Friedman test)
Exudated serum albumin	–	0.354 ± 0.06	–	0.356 ± 0.03	NS (Wilcoxon test)

Note: *Mean ± standard deviation.
Abbreviations: OSDI, Ocular Surface Disease Index; TFBUT, tear film break-up time; NS, not significant.

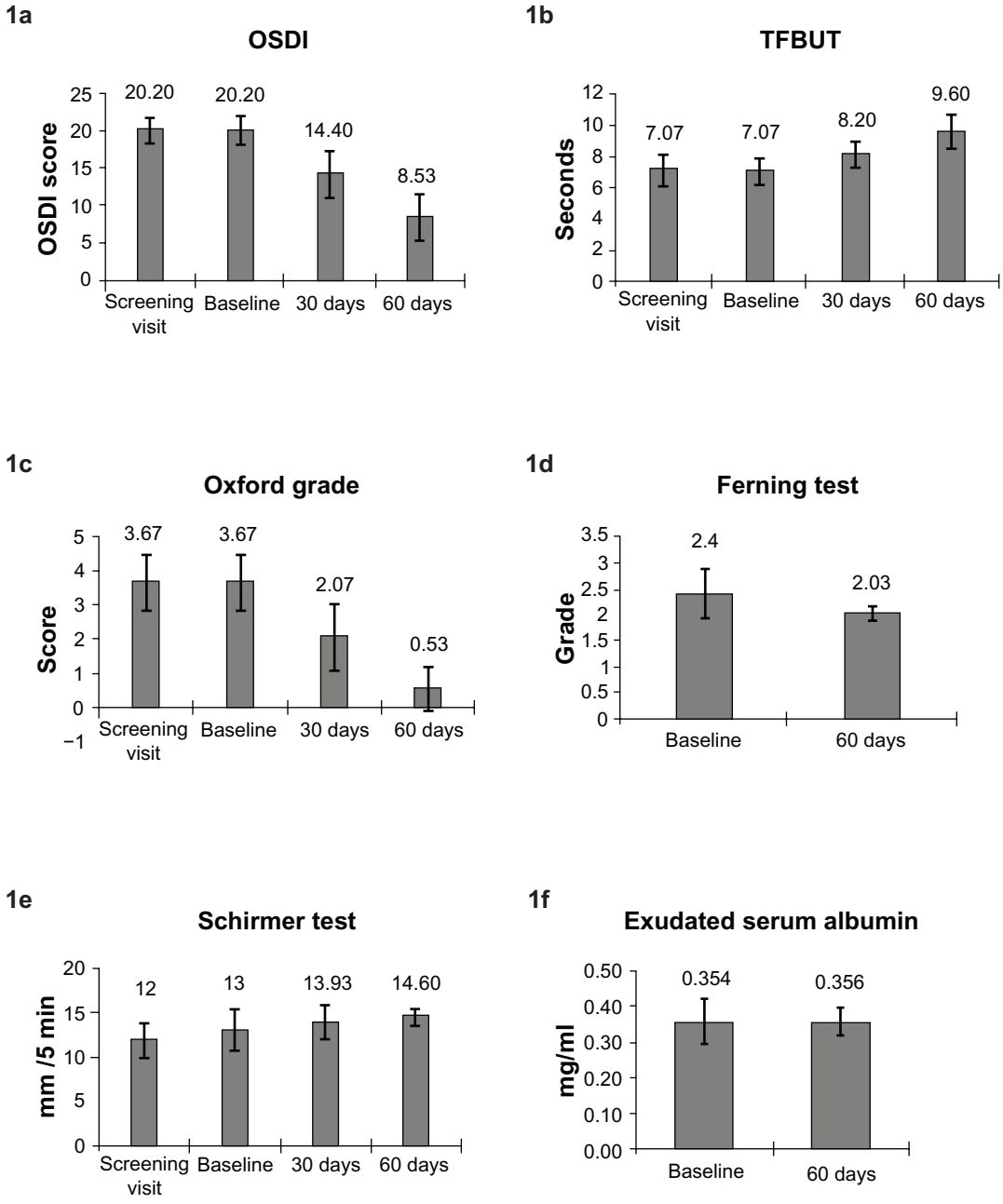

Figure 1 Data for each variable and standpoint analyzed are graphed (mean ± SD).

TSP suitable for management of signs and symptoms of dry eye. Hyaluronic acid (also termed sodium hyaluronate) is a non-Newtonian polymer which shows a good retention time on the ocular surface, has viscosity already at low concentration, thus reducing rubbing stresses during blinking and stabilizing tear film, thereby delaying tear evaporation.[25]

The action of these two agents in separate formulations has been investigated in the past[26,27] in dry eye related to contact lens wear. To our knowledge, the present research is the first to analyze the synergistic effect of a new formulation containing both agents used in contact lens wearers.

Contact lens wearers having a replacement regimen less than one month were selected for this study because this time schedule is becoming popular in many countries.[28] As already reported, discontinuation of contact lens wear is strictly related to onset of symptoms of discomfort, which reduce daily wear at first, and then progresses to abandonment of contact lens wear if management and therapy are unsuccessful.[4]

Patients included in our study had worn contact lenses continuously for five years or more, and about than half of them had experienced previous intolerance to contact lenses.

All patients exhibited good compliance with Xiloial treatment, with optimal tolerability and no adverse effects. In this respect, no blurring, itching, or scratching after the trial instillation were reported by any patient while wearing their contact lenses.

A statistically significant reduction in subjective symptoms was observed after one month of treatment, and in 12 of 15 patients the OSDI value reached the normal symptom score at the endpoint. In our opinion, residual subjective symptoms could be related to the never stopped contact lens wear in itself, although no relationship with the contact lens regimen was found.

A statistically significant increase in TFBUT values was demonstrated in all patients stepwise with duration of treatment, but no subject reached the normal TFBUT value of higher than 10 seconds. On the other hand, continued wearing of contact lens during treatment could account for these results, because a decrease in TFBUT is recognized as a major side effect of contact lenses.[29]

Seven of 15 patients showed a normal tear ferning grade at baseline, even in the presence of subjective symptoms of discomfort, which appears to be in disagreement with previous authors who have shown tear ferning to be a good predictor of successful tolerance to contact lens wear.[30] As previously suggested,[21] the interpretation of tear ferning appears to be related to the ionic content in tears. In this study, tear ferning appeared significantly reduced compared with normal values after treatment, possibly due to tear dilution performed by the substitute.

Both corneal and conjunctival surface epithelial damage were significantly reduced already after one month of treatment, and complete epithelial healing was shown in 19 of 30 eyes at the endpoint. This result is particularly interesting if one considers that epithelial integrity was restored after treatment, even in the presence of contact lens wearing onsite. This observation supports the mucomimetic action of Xiloial, and its ability to perform a protective role as a polymer interposing between the corneal epithelium and the contact lens.

Patients had been selected ad hoc with normal Schirmer I values as an inclusion criterion for this study in order to reduce study variables and to enrol patients with mild subjective discomfort. A small, but statistically significant, increase in Schirmer value was noted at endpoint versus baseline. However, the reliability of the Schirmer test has been debated recently due to the large coefficients of variation in repeated measures, unless for values lower than three mm wet strip length.[31] Therefore, it is feasible that the 2 mm increase in Schirmer values observed in our study is related more to test variability than to treatment efficacy.

Serum albumin in tears is considered to be an indirect index of inflammation as a consequence of passive exudation due to increased leakage from blood vessels.[32] Increased serum albumin levels in contact lens wearers' tears are already reported in the literature and, the higher the concentration, the greater the degree of deposition that can be expected on the lens, particularly for dry eye.[33] Paired statistical analysis of all patients did not show any statistically significant differences in serum albumin content in tears. Interestingly, a significant decrease in exudated serum albumin was only shown in the subgroup of patients who had not previously reported single or repeated episodes of intolerance to contact lens wear. A slight, but not significant, increase was shown in the subgroup of patients who reported previous intolerance to contact lenses. We recognize that no conclusions can be drawn from the present study due to the limited number of patients, but it can be speculated that the conjunctival response may change after intolerance, as has been suggested for overnight contact lenses.[34]

As a concluding remark, a two-month treatment with the newly formulated copolymer Xiloial® in symptomatic dSCL wearers still wearing the device showed:

- high tolerability
- reduction in subjective symptoms
- reduction in ocular surface epithelial damage
- increase in TFBUT value
- reduction of exudated serum albumin in tears in about half of patients.

Disclosure

The investigators have no proprietary interest in the tested product. No financial arrangements have been made where study outcome could affect compensation.

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