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CASE REPORT

Early results on the use of chitosan-*N*-acetylcysteine (Lacrimera®) in the management of dry eye disease of varied etiology

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Abstract

Purpose To evaluate the effect of once daily administration of chitosan-*N*-acetylcysteine (Lacrimera®) in the management of dry eye disease (DED).

Methods Eighteen patients (3 male, 15 female) aged 25–86 years (mean 61.1) and suffering from moderate to severe DED with superficial punctate keratitis (SPK) were retrospectively evaluated after a trial of Lacrimera® drops (1 drop in the morning for 5 days only). All the patients were using other artificial tears before the treatment. All lubricants were stopped, and Lacrimera® was started instead. Slit-lamp examination and images were taken before and at 1 and 3 weeks follow-up after the treatment. The subjective (Ocular Surface Disease Index, OSDI) and objective (Oxford Grading System, OGS) evaluation was recorded. A paired student's *t* test was performed to analyse the data.

Results At baseline, the SPK grade was I to IV (OGS) and the OSDI ranged from 25 to 71.4. Fifteen patients showed a statistically significant ($p < 0.0001$) improvement in OGS and the OSDI at 3 weeks post-treatment. Three patients showed no improvement.

Conclusions A single-dose instillation of chitosan-*N*-acetylcysteine for five consecutive days improved signs and symptoms in patients affected from DED from a variety of causes, who were refractory to standard treatment with lubricants. Given its posology, the absence of side effects and the results obtained Lacrimera® should be taken into consideration as a viable option in patients with moderate to severe DED.

Keywords Dry eyes disease · Management · Artificial drops · Symptoms

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Introduction

Dry eyes disease (DED) is a common condition. There are many factors that can lead to symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface (OS) [1]. Considering the global prevalence, DED is a public health issue with huge clinical and economic impact.

Health and integrity of the OS-lacrimal functional unit (LFU), which is composed of the cornea, conjunctiva, accessory lacrimal and meibomian glands, the main lacrimal glands, the blink mechanism and the sensory (via the trigeminal nerve to the central nervous system) and motor nerves (sympathetic and parasympathetic fibres) [2], is critical for sight.

Classically, the tear film is composed of three layers, mucin, aqueous and lipid, though latterly the

distinction between the mucin and aqueous layers is reported to be less well defined with the two merging in a gradient rather than as distinct layers. Maintaining a healthy and comfortable ocular surface requires stability of the whole system. A malfunction of any of the LFU components can lead to DED.

Typically, DED is divided into two subtypes: aqueous tear-deficient dry eye (ADDE) and evaporative dry eye (EDE). The diagnosis of DED is based on clinical history and symptoms supported by a number of tests that can provide additional information. The diagnosis is often a challenge on account of the disconnect between symptoms and signs, which often do not correlate and the overlap between normal and abnormal values of the diagnostic tests such as Schirmer's test, tear film break-up time and tear meniscus height. Tear osmolarity has been proposed as being more specific, but clinical experience shows that even with this test there is an overlap with some symptomatic patients having low osmolarity and vice versa [3].

Treatment options for DED are multiple and manifold, reflecting the challenge posed by a disease of varied etiology, complex pathology and symptomatology. Artificial tear drops are the mainstay. These provide relief, but this is often temporary requiring frequent instillation of drops, which in turn impacts on the quality of life (QoL) and compliance. Inflammation has been identified as a major underlying factor in DED, and topical short-term steroids or long-term non-steroidal anti-inflammatory drops, namely cyclosporine 0.05–0.1%, have gained prominence in the therapy of DED. Interventions such as punctal occlusion with plugs or cautery, contact lenses and tarsorrhaphy are options in severe and refractory cases [4–8].

In this retrospective study, we evaluated the efficiency of the dry eye medication Lacrimera® [9], which requires only once-a-day instillation, (CROMA-PHARMA GmbH, 2100, Leobendorf, Austria) in the management of the DED. Lacrimera® is based on a chitosan biopolymeric backbone, which is modified by the introduction of *N*-acetylcysteine (NAC) via nucleophilic substitution.

Chitosan is a well-characterised polycationic polysaccharide derived from alkaline deacylation of chitin and exhibits low toxicity and excellent biocompatibility. *N*-acetylcysteine, which is a derivative of amino acid L-cysteine, also has been used to treat corneal and external eye diseases [9].

Methods

Eighteen patients (3 males, 15 females) with moderate to severe DED were treated with Lacrimera®. Their age ranged from 25 to 86 years (mean 61.1). All patients had SPK (Table 1) and were already using artificial tears with no or minimal benefit in both symptoms and signs. Slit-lamp evaluation (Haag Streit, Edinburgh Way, Harlow, Essex, UK) and images (Topcon Great Britain Ltd., Kenneth Side, Newbury Berkshire, UK) with yellow barrier filter were taken for all patients before and 1 and 3 weeks after treatment. A subjective (Ocular Surface Disease Index, OSDI) and objective (Oxford Grading System, OGS) evaluation was carried out in all patients at baseline and after use of Lacrimera®. Statistical analysis for OSDI between pre- and post-treatment group (3 weeks) was performed with paired student's *t* test using graph pad prism software version 7.0 (Graph Pad, Inc.).

Treatment regime All concomitant artificial tear drops were discontinued and Lacrimera® administered once a day, to each eye for 5 days only. Patients were requested to record the daily administration of medication and bring back any unused vials.

Results

At baseline, the SPK grade was I to IV (OGS) and the OSDI ranged from 25 (mild) to 71.4 (severe) (Table 1). After 3 weeks, there was a significant improvement in the OSDI and OGS in 15 patients: $p < 0.0001$ with mean difference of 18.11 and 95% confidence interval ranging from 11.46 to 24.77. In all the 15 cases, the improvement was noted in both the OSDI and OGS (Fig. 1). In three patients, no improvement was noted, neither in the OSDI nor in the OGS (Table 1). All patients had used the drops as prescribed but not consistently at the same time every day.

Discussion

Among the different treatment options available on the market for DED and ocular surface disease, lubricants and anti-inflammatory drugs are undoubtedly the most frequently used products. Lubricants, however, can only suppress symptoms temporarily. It is well known though that chronic use/abuse of topical steroids can

Table 1 Patient demographics, diagnosis and severity of dry eye disease pre and post treatment

General information				OSDI		OGS	
Patient	Age	Gender	Associated condition	Pre	Post (3 weeks)	Grade pre	Grade post (3 weeks)
1	62	F	Granular dystrophy, corneal grafts	62.5	31.3	III	I
2	58	M	Persistent epithelial defect, glaucoma	55.6	41.7	II	I
3	81	M	Ocular cicatricial pemphigoid, persistent epithelial defect	53.6	35.7	III	II
4	79	F	Glaucoma	46.9	31,3	II	I
5	58	F	Lasik	71.4	17.9	IV	0
6	49	F	Rheumatoid arthritis	35.7	17.9	II	I
7	52	M	Epithelial defect, Neurotrophic keratopathy	25	12.5	I	0
8	74	F	Superior limbic keratitis	22.7	11.4	II	I
9	83	F	Rheumatoid arthritis	50	25	III	I
10	69	F	Dry eyes	45.5	11.4	III	0
11	81	F	Ocular cicatricial pemphigoid, glaucoma, dry eyes	55.6	41.7	II	I
12	86	F	Interstitial keratitis	55.6	55.6	III	III
13	25	F	Corneal graft, dry eyes	46.9	31.3	III	II
14	36	F	Neurotrophic keratopathy	46.9	46.9	II	II
15	54	F	Limbal stem cell deficiency	41.7	41.7	II	II
16	63	F	Corneal decompensation	37.5	25	II	I
17	54	F	Glaucoma	46.9	15.6	III	0
18	36	F	Neurotrophic keratopathy	41.7	21.8	II	I

OSDI Ocular Surface Disease Index, *OGS* Oxford Grade System, *F* female, *M* male

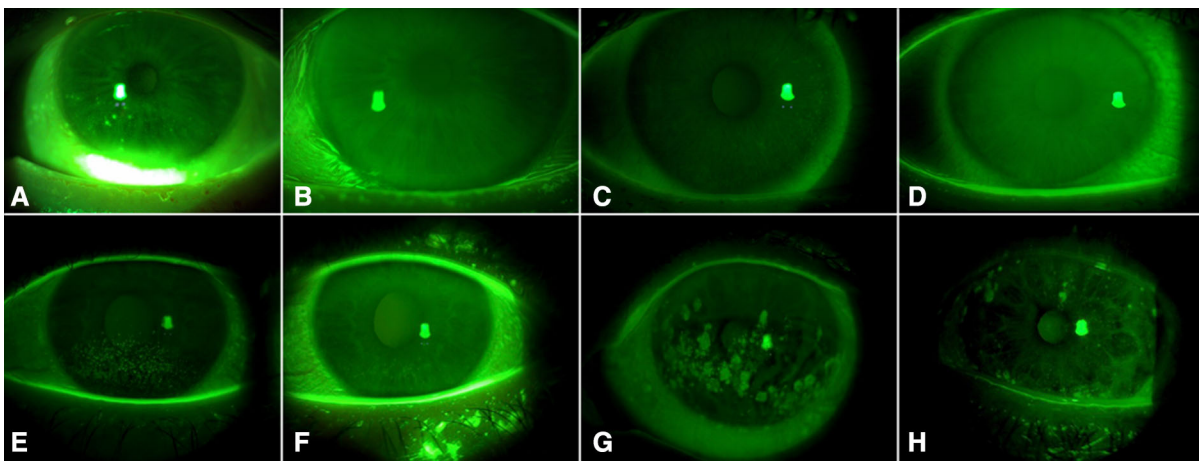

Fig. 1 Slit-lamp images taken with diffuse illumination and yellow barrier filter showing corneal fluorescein staining of different grade in four different patients (4, 9, 10 and 17 in Table 1) before (**a**, **c**, **e**, **g**) and after (**b**, **d**, **f**, **h**) treatment with Lacrimera® drops

lead to severe side effects such as cataract and glaucoma.

In our cases, we ascertained the efficiency of chitosan-*N*-acetylcysteine eye drops (Lacrimera®) in the management of SPK in eyes with different backgrounds and we based our findings on the OSDI and OGS. OSDI has been proven to be a reliable questionnaire in assessing the severity of ocular surface symptoms (from mild to severe) [10], and the OGS is

widely used as an effective objective indicator of DED signs.

We found that Lacrimera® was able to reduce signs and symptoms in most of our cases with good compliance and tolerability, despite the varied nature of the underlying cause. No adverse events were recorded over the 3-week period. This data confirms findings of a recently published clinical study with Lacrimera® in dry eye patients [9] but also suggests that the indications for use of Lacrimera® can be expanded to other ocular surface pathology associated with dry eyes. We found the ocular surface to be healthier 1 week after treatment as indicated by significant reduction of SPK in severe dry eye patients. This treatment is meant to be efficient for up to 3 weeks after stopping the drops after 5 days application. Recent clinical data from this study indicate special properties of chitosan-*N*-acetylcysteine eye drops, which help to form a long-lasting protective layer on the ocular surface for up to 3 weeks, thus stabilising and restoring the tear film. New biopolymer technology on which Lacrimera® is based may overcome limitations of artificial tears by interacting with the polymer–mucin network on the ocular surface. In particular, covalent interactions of free thiol moieties originating from chitosan-*N*-acetylcysteine and from mucosal glycoproteins produce an artificial glycocalyx-like structure on the eye. This in turn may lead to an enhanced stability of the polymer–mucin network [9].

Having to apply only one drop per day and for only 5 days, not only will lead to better compliance and quality of life but can also reduce the cost of management. In dry eyes, including some associated with a diverse range of pathology such as corneal grafts, glaucoma and glaucoma medication-related dry eyes, corneal dystrophy and others listed in Table 1, Lacrimera® worked very well in reducing both signs and symptoms. The three cases that did not respond had limbal stem cell deficiency, neurotrophic keratopathy and interstitial keratitis, respectively. This might be a reflection of the underlying condition where the pathology is more complex and the corneal epithelium is more vulnerable.

It is likely that patients would continue to benefit from use of Lacrimera® on an ongoing basis beyond the 3-week period tested in this study. Further studies need to be carried out in order to confirm the efficacy and safety of the use of Lacrimera® over a longer duration, in larger number of patients, for each underlying pathology tested. Many patients had requested a second course of the medical device and given the results obtained Lacrimera® should be taken into consideration as a viable option in patients with moderate to severe DED.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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