

## Treatment of Moderately Severe Sjögren's Syndrome-Related Dry Eye without Immunomodulation: A Self-Controlled, Unmasked Study

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### Abstract

Our aim was to demonstrate if mild objective and moderate or severe subjective symptoms of the Sjögren's syndrome-related dry eye could be diminished without the use of any anti-inflammatory agents.

Altogether 21 patients (18 female, 3 male) were enrolled into our prospective, unmasked, self-controlled study. The mean age of the patients was  $60.4 \pm 11.4$  years. The inclusion criteria were: lid parallel conjunctival folds (LIPCOF)  $\geq$  grade 1, lissamine green staining (Oxford scheme grade)  $\geq$  grade 1, decreased basal tear secretion  $\leq$  5mm, moderate or severe subjective symptoms [ocular surface disease index (OSDI)  $\geq$  23], diagnosis of Sjögren's syndrome. During the study period, the subjects used a study drug (Con-heal® eye drops), that is a preservative-free, unit-dose artificial tear, containing isotonic glycerol and 0.015% sodium hyaluronate four times a day for three months.

The three-month long use of the study drug resulted in a significant decrease of the LIPCOF degree from an initial value of  $2.48 \pm 0.75$  on the right eyes and  $2.57 \pm 0.75$  on the left eyes to  $1.33 \pm 0.73$  and  $1.38 \pm 0.67$ , respectively. The initial lissamine green staining of the eye surface also decreased significantly from  $1.76 \pm 0.89$  and  $1.95 \pm 0.86$  to  $0.29 \pm 0.56$  and  $0.29 \pm 0.56$ , respectively. There was a significant decrease in the OSDI values from  $55.81 \pm 15.19$  to  $32.54 \pm 19.51$ . Basal tear secretion did not change significantly from an initial value of  $1.6 \pm 1.4$  mm on the right and  $1.7 \pm 1.4$  mm on the left eyes.

Our results show that the three months use of the study drug resulted in a significant improvement of the subjective and objective symptoms of the Sjögren's syndrome-related dry eye, without the need of any traditional anti-inflammatory agents and without significant improvement in the basal tear secretion. We suspect, based on in vitro experiments, that isotonic glycerol-induced decrease of HLA-DR expression may be responsible for this favorable effect.

**Keywords:** Sjögren's Syndrome; Dry Eye; Immunomodulation

### Introduction

Sjögren's syndrome is a chronic autoimmune disease with a prevalence of 0.2 to 1.2% [1]. Ninety percent of the patients is female [1]. As a result of the chronic inflammation, the pronounced lymphocytic infiltration of the exocrine glands may be observed during histological examinations. The chronic inflammation leads to the decreased secretion of the exocrine glands. Any type of the exocrine glands may be affected; dry eye and dry mouth are the leading symptoms. The Sjögren's syndrome may cause serious aqueous-deficient dry eye, as the lacrimal glands are affected.

Sjögren's syndrome may be primary and secondary, depending the syndrome is associated to any other autoimmune diseases. The distribution of the primary and the secondary Sjögren's is half to half [1].

About 12% of the aqueous deficient dry eye patients are diagnosed with Sjögren's syndrome. The Sjögren syndrome patients have significantly worse eye surface staining, lower Schirmer results and higher OSDI scores than those dry eye patients who do not have Sjögren syndrome [2].

We reported earlier that the investigated study drug, containing isotonic glycerol and sodium hyaluronate, had decreased chronic inflammation causing conjunctivochalasis [3] and had reduced eye surface staining [4]. In our current paper, we would like to demonstrate, if the same monotherapy was effective to reduce the subjective and the objective signs of dry eye among the Sjögren's patients with a significant change in the primary endpoint, the decrease in the eye surface staining.

## Patients and Methods

### Patients

Twenty-one adult patients from the patients of the Corneal and Eye surface diseases outpatient unit of the Department of Ophthalmology at the Semmelweis University between 1st February 2016 and 24th October 2016 were enrolled into our prospective study approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (permission No. 265/2015 given on 16th December 2015). The research followed the tenets of the Declaration of Helsinki. All participants gave their written informed consent to the examination. The trial was registered at the ISRCTN database (registration number: ISRCTN17717813) after the completion of the study, since trial database submission is not compulsory in Hungary before starting such a single center study involving only a few patients. The authors confirm that all ongoing and related trials for this drug are registered.

Eighteen female and three male patients participated in the study with a mean age of  $60.4 \pm 11.4$  years (between 44 and 79 years of age). The number of the required patients was determined by power analysis, described in detail in our previous paper [3].

Patient inclusion criteria were voluntary participation above 18 years of age, LIPCOF degree 1 or higher, lissamine green staining of minimum grade 1 or higher on the Oxford Scheme grade, decreased tear secretion with topical anesthesia less than 5 mm/min, moderate or severe subjective symptoms with an OSDI score higher than 23, and former diagnosis of Sjögren's disease. None of the patients has received general immunomodulation therapy. And none of the patients had blepharitis. Exclusion criteria included pregnancy or lactation, pterygium, prolonged treatment with eye drops with the exception of artificial tears, active allergic keratoconjunctivitis, current keratitis or conjunctivitis of infectious origin, surgery affecting the eye surface, as well as eye injuries occurred within 3 months before starting the treatment. Most of the patients have already used commercially available artificial tears regularly (17 out of the 21 for at least one month) before entering the study. We did not use a wash-out period, as not all the patients have used artificial tears before, and in those patients formerly using artificial tears, both objective and subjective symptoms of the dry eye remained. The improper previous treatment with artificial tears, those were unable to control the dry eye symptoms of the patients or the lack of the previous artificial tear treatment makes the trial self-controlled. The results after the treatment with the study drug can be compared to the results of the enrolment visit.

### Description of treatments and examination

The treatment and most of the examinations were similar as described in our former trial [3], in that we examined the conjunctivochalasis-decreasing effect of the study drug, therefore the examinations and the treatment is briefly summarized in this current paper. At the first visit the required number of unit-doses of the study drug (Conheal® eye drops), that is a preservative-free, inorganic salt-free artificial tear (provided by Pannonpharma Ltd., Pécsvárad, Hungary), containing isotonic glycerol and 0.015% hyaluronic acid in purified water [3,4] were given to our patients. Patients were instructed to apply the study drug on both eyes four times a day during the three months of the study. Due to the prior use of artificial tears and/or significant subjective dry eye symptoms before the trial and the detailed discussion of the study at the first visit, as well as during the one-month and three-months-visits the patients were asked to report any adverse events.

The subjective complaints of the patients, as well as the impact of the dry eye complaints on their everyday life were recorded by the help of the OSDI questionnaire [8]. Patients were asked to self-complete the OSDI questionnaire translated and validated into Hungarian [9] after receiving general instructions.

On the one-month visit all the tests except the Schirmer's test were repeated, and at the three-months visit all the tests were performed again.

Tear film break up time was not recorded, as in our previous trial with the study drug we had found a statistically significant, but clinically not significant effect on TF BUT [3,10].

To increase the validity of the measurements all measurements were performed by the same person during the whole study. Measurements were supervised by an independent expert in a randomly selected 30% of the cases. The independent expert was not aware of the stage of the patient, when performing the analysis. Both the investigator and the independent expert had a Good Clinical Practice Certificate.

### Statistical evaluation

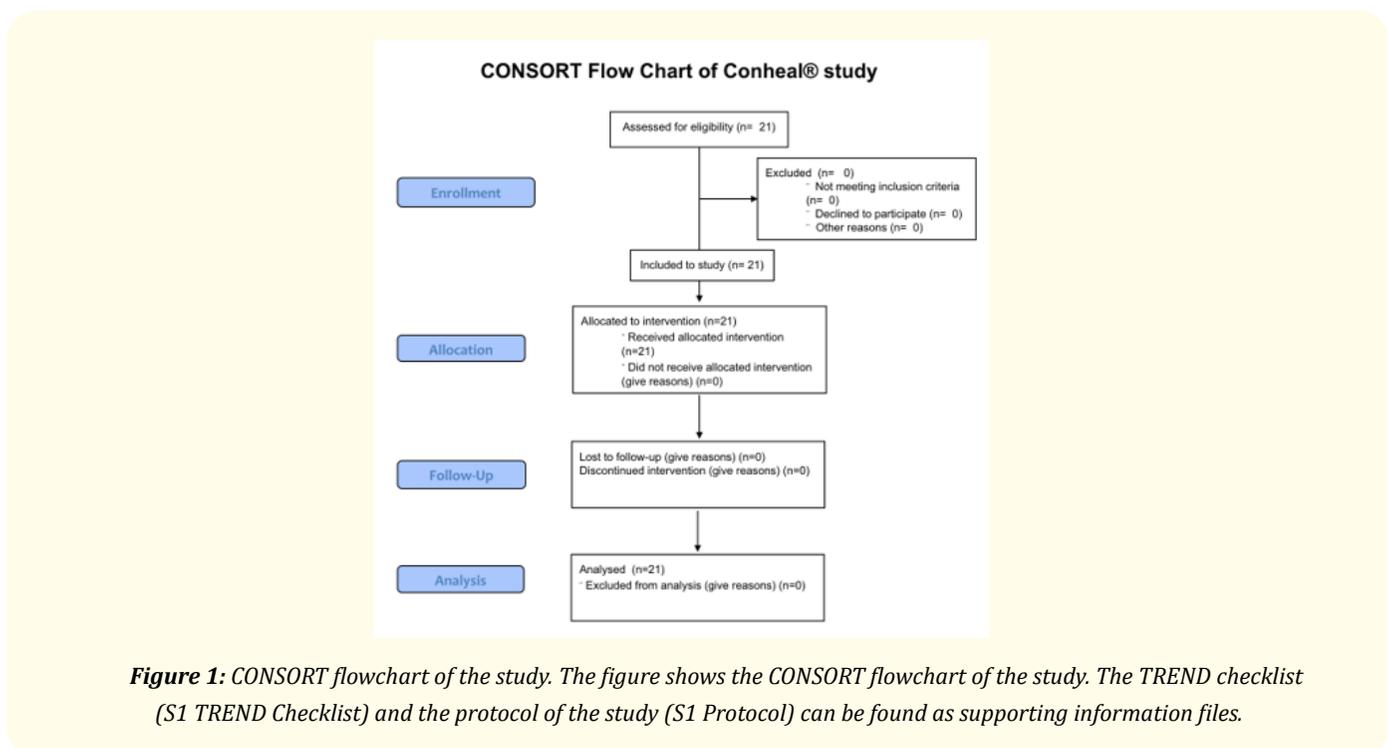
The sample size for the study was evaluated by post hoc power analysis. LIPCOF degree, Oxford grade and OSDI score were tested. For a conservative power estimation, the highest observed within-group standard deviation of 0.9 was supposed, and a low correlation value of 0.2 was assumed for correlated measurements performed on the same subject at month 0 and month 3.

The results of the objective and subjective tests recorded at the first visit were compared to the results of similar examinations after one and three months of treatment. Additionally, results after one month of treatment were compared to the results after three months of use of the study drug (except for Schirmer’s test, that was not performed on the one-month visit). For the comparison of ordinal data (LIPCOF degree, Oxford Scheme grade) and non-normally distributed data (OSDI) the non-parametric Wilcoxon Signed Rank Test was used, meanwhile the normally distributed data (Schirmer’s) were compared by the help of the parametric Paired T Test using the SPSS Statistics 22 software (IBM Corporation, Armonk, NY, USA). The results were expressed as mean ± standard deviation for each objective test and separately for the right and the left eyes. The OSDI test represents the personal satisfaction from the treatment of both eyes.

Since this was an exploratory study no adjustment for multiplicity was made, although the primary outcome measures were tested both at the right and the left eye.

**Result**

Figure 1 shows the CONSORT flow chart of the study. The TREND checklist (S1 TREND Check- list) and the protocol of the study (S1 Protocol) can be found as supporting information files. Study details are given in the Methods section.



**Figure 1:** CONSORT flowchart of the study. The figure shows the CONSORT flowchart of the study. The TREND checklist (S1 TREND Checklist) and the protocol of the study (S1 Protocol) can be found as supporting information files.

The numerical results of the examinations are summarized in table 1, as starting visit, one-month-visit and three-month visit. The results of the starting visit are compared to the one-month- and three-month-visit, and the results of the one-month-visit is compared to those of the three-month-visit, where it was applicable.

	Month 0*		Month 1*		Month 3*		Month 0-1		Month 0-3		Month 1-3	
	mean ± SD		mean ± SD		mean ± SD		P value**		P value**		P value**	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
LIPCOF degree	2.5 ± 0.8	2.6 ± 0.7	1.6 ± 0.7	1.7 ± 0.7	1.3 ± 0.7	1.4 ± 0.7	< 0.001	< 0.001	< 0.001	< 0.001	0.025	0.014
Oxford grade	1.8 ± 0.9	1.9 ± 0.9	0.9 ± 1.0	0.8 ± 1.0	0.2 ± 0.6	0.3 ± 0.6	0.001	< 0.001	< 0.001	< 0.001	0.018	0.029
Modified Schirmer’s test	1.6 ± 1.4	1.7 ± 1.4	N/A	N/A	1.8 ± 1.5	1.8 ± 1.5	N/A	N/A	0.384	0.452	N/A	N/A
OSDI Score	55.8 ± 15.2		37.7 ± 20.0		32.5 ± 19.5		0.001		<0.001		0.005	

**Table 1:** Characteristic measures of the dry-eye syndrome after one- and three months treatment with the study drug.

\*: LIPCOF degrees, Oxford Scheme grades, modified Schirmer’s test, and OSDI scores were measured, and statistical analysis was performed as described in Methods.

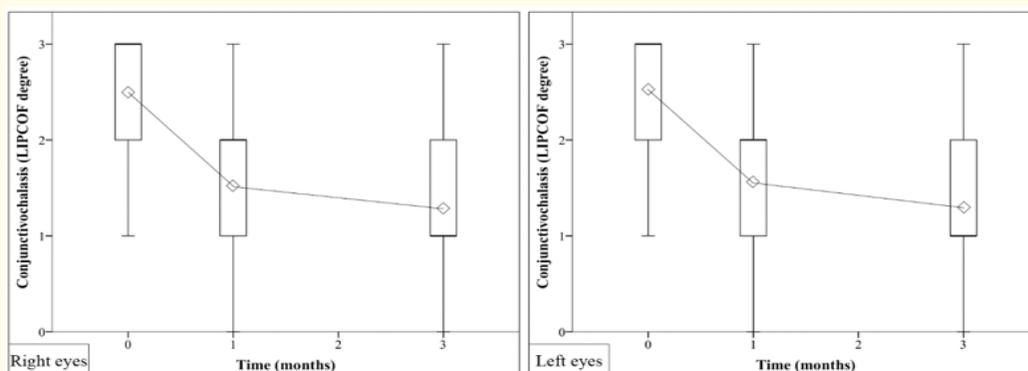
\*\*: P-value of the Wilcoxon Signed Rank Test for LIPCOF, Oxford and OSDI, and P-value of the paired T test for modified Schirmer’s.

The results of the post hoc power analysis are summarized in table 2. The results in the table indicate that there was enough power (> 0.80) to show significant differences between months.

	Month 1 vs. Month 0	Month 3 vs. Month 0
LIPCOF degree	1.0	1.0
Oxford grade	0.99	1.0
OSDI score	0.99	0.99

**Table 2:** Results of the post hoc power analysis.

The conjunctivochalasis, measured in LIPCOF degrees were significantly decreased in both eyes after one and three months of the treatment. The study drug decreased the conjunctivochalasis after one and three months of treatment (Figure 2).

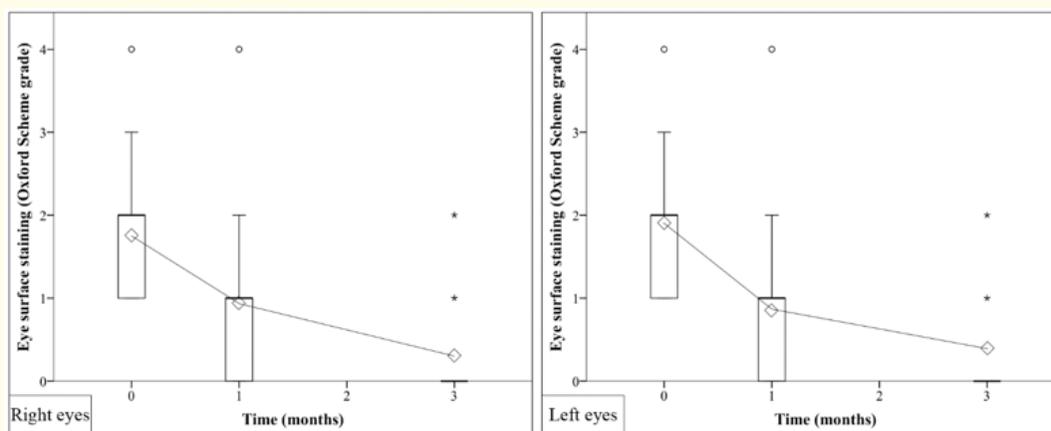


**Figure 2:** Degree of the conjunctivochalasis in terms of LIPCOF degrees after 1 and 3 months of the treatment.

The study drug caused a significant decrease of LIPCOF degree on both eyes after one- and three months treatment.

Means and their standard errors of the LIPCOF degree are shown, the distribution of the data is expressed by the help of box plots also.

The most prominent change was detected in the eye surface staining, described by the Oxford Scheme grade. The improvement was significant after one- and three-months treatment (Figure 3).

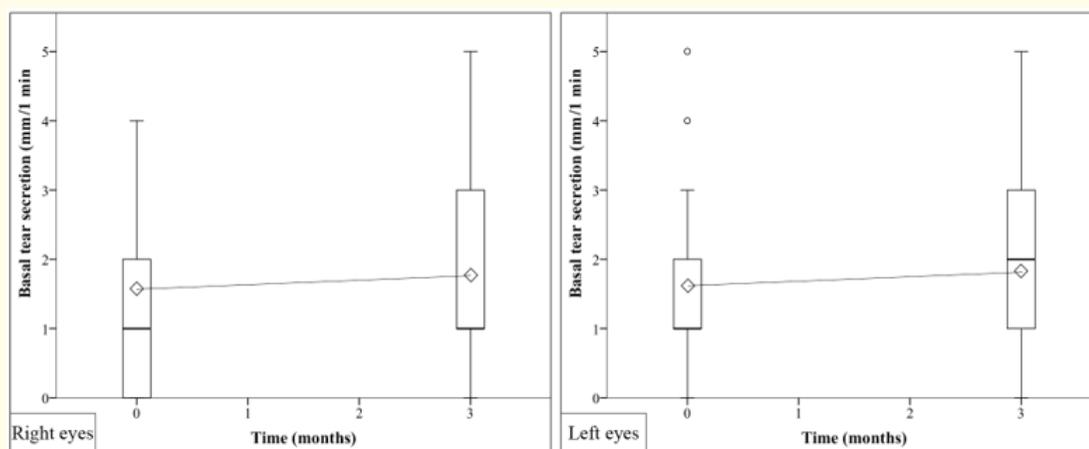


**Figure 3:** Degree of the eye surface staining in terms of Oxford Scheme grade after 1 and 3 months of the treatment. The study

drug caused a significant decrease of the eye surface staining on both eyes after one- and three months treatment. Means and their standard errors of the Oxford Scheme grade are shown, the distribution of the data is expressed by the help of box plots also.

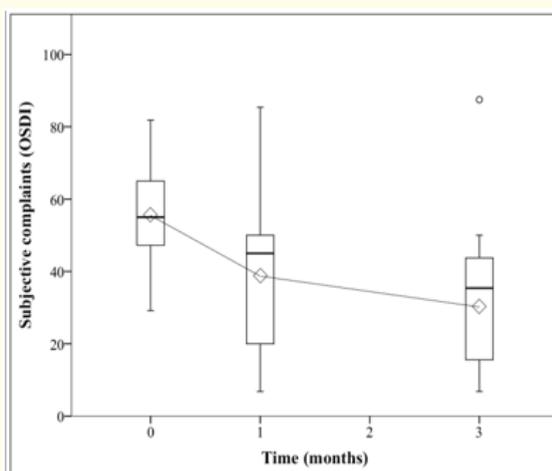
On the box plot outliers are identified as "out" values (small circle) and "far out" values, marked by asterisks.

The basal tear secretion, that was expressed as millimeters/minute did not change significantly during the study period (Figure 4).



**Figure 4:** Basal tear secretion after 3 months of the treatment. The study drug did not change the basal tear secretion during the study period. Means and their standard errors of the one-minute anesthetic Schirmer's values are shown, the distribution of the data is expressed by the help of box plots also. On the box plot outliers are identified as "out" values marked by small circles.

The subjective symptoms of the patients, measured by the help of the OSDI questionnaire, decreased significantly after one- and three-months use of the study drug. The longer use of the study drug was beneficial on the subjective symptoms, as the OSDI-score decreased significantly from the one-month values to the three-months results (Figure 5).



**Figure 5:** The subjective symptoms expressed as OSDI-score after 1 and 3 months of the treatment. The study drug caused a significant decrease of OSDI-score after one- and three-months treatment, between the one- and three-months visit further significant change was found. Means and their standard errors of the Oxford Scheme grade are shown, the distribution of the data is expressed by the help of box plots also. On the box plot outliers are identified as "out" values marked by small circles.

During the study period no adverse reactions were reported; patients' compliance was very high throughout the whole study.

## Discussion

In the course of our study the preservative-free, inorganic salt-free, isotonic glycerol and 0.015% sodium hyaluronate containing study drug administered four times a day significantly improved the objective and subjective symptoms of the dry eye patients suffering Sjögren's syndrome without the need for any traditional anti-inflammatory agents.

There is no general formula, but a broad spectrum to treat the dry eye accompanying Sjögren's syndrome [11]. The therapy is based on the severity of the disease and on the response to the added therapy [12]. The first line topical treatment of dry eye patients is the chronic use of the substitution of the aqueous sub-phase of the tear film [13,14]. If symptoms persist and/or corneal complications occur, topical and/or systemic anti-inflammatory therapy is introduced. To improve the effect of the eye drops or if conservative therapies fail, fitting of bandage contact lenses [15] or surgical interventions (e.g. punctal occlusion [16]) shall come to mind.

When the use of artificial tears is advised, the physician shall suggest the best artificial tear, that suits the condition the best, as the choice from the over the counter artificial tears is difficult for the patient, and marketing of the artificial tears may influence them. In case of Sjögren's syndrome-related dry eye, artificial tears containing lubricants are the suggestions [12]. Avoiding the traditional preservatives, as benzalkonium chloride and EDTA, is important if the patient needs to use artificial tears for at least 6 times a day [17] as they are potentially toxic to the eye surface [12].

Another option to ameliorate the state of the damaged ocular surface is the use of the autologous serum preparation. In Sjögren's syndrome-related dry eye the use of autologous serum improves symptoms and confocal microscopy findings [18]. Autologous serum or own blood preparations decrease both subjective and objective symptoms significantly [19].

In case of serious symptoms and/or corneal complications anti-inflammatory therapy may be introduced. The use of topical corticosteroids leads to the rapid decrease in the objective and subjective symptoms of the dry eye [12,20]. Mild topical corticosteroids are effective to rule the inflammation, but in a long-term use severe side-effects (e.g. cataract formation and glaucoma) threaten the visual functions of the patients [21].

For an effective, long-term, and less dangerous immunomodulation topical cyclosporine (like Ikervis or Restasis) and lifitegrast (Xiidra) are prescribed. Both drugs effect the function of lymphocytes. Cyclosporine inhibits calcineurin, that activates the transcription of interleukin-2 [22], while lifitegrast inhibits an integrin, the (like lymphocyte function-associated antigen 1 (LFA-1) [23]. By decreasing the inflammation of the ocular surface and of the lacrimal gland, these eye drops may increase tear secretion [24]. Through cyclosporine may have many side effects, burning, stinging, and foreign body sensation. The results of a meta-analysis show, that cyclosporine eye drops have a higher side effect rate, than the control drops without the active ingredient [25]. While using lifitegrast, burning, instillation site reaction, reduced visual acuity, dry eye, and change in taste may occur [26].

The study drug was chosen due to its favorable effect on corneal staining [3,4] and on conjunctivochalasis [3]. The special feature of the study drug is its isotonic glycerol concentration. It is known from the literature that in dry eye, the human leukocyte antigen-DR (HLA-DR) expression level on the surface of the conjunctival epithelial cells is elevated, and it correlates with the eye surface staining. Even the efficacy of the dry eye disease treatment may be assessed by measuring the HLA-DR expression levels [27]. The HLA-DR expression levels are extreme high in Sjögren's syndrome-related dry eye [28]. It is known, that in epidermal keratinocytes isotonic glycerol decreases the toll-like receptor 2 (TLR2) and TLR3 activation caused upregulation of the expression of HLA-DR [29]. Thus, it is possible that the study drug decreases the severity of the conjunctivochalasis and corneal staining through lowering the HLA-DR expression level on the conjunctival epithelial cells. The study drug also contains hyaluronic acid, that retains water on the ocular surface, and improves lubrication [30]. Sodium hyaluronate has well-established efficacy for the treatment of dry eye syndrome. It is the salt of hyaluronic acid, an endogenous compound that plays an important role in regulating cell behavior during various morphogenic and restorative biological processes. Circulating serum levels in man are reported in the range of 10-100 µg/L [31] and its effectiveness in increasing tear film break-up time and protecting the corneal epithelium is well documented [32,33]. Besides, hyaluronic acid might elongate the retention time of glycerol on the ocular surface, thus increasing its therapeutic effect [34]. These effects of the isotonic glycerol and the hyaluronic acid together are potentially responsible for the favorable changes the study drug has on the eye surface. The lack of preservatives improves the long-term use and compliance of the drop [35].

In course of our study, the study drug was able to diminish the corneal staining almost completely and improved the other objective and subjective symptoms of the dry eye, as well, except the basal tear secretion. Our results are in agreement with the results of two earlier clinical studies performed with the same study drug. In the first article [4] they also showed, that the improvement of the rose bengal staining lead to improved personal satisfaction. We demonstrated the decrease in the eye surface staining by lissamine green in our former paper [3,10]. In agreement with earlier studies carried out with sodium hyaluronate containing products, the epithelial damages were resolved due to the reduction of chronic harms of the corneal epithelium [33]. The LIPCOF degree, that correlates well with the subjective symptoms [36] of the dry eye decreased in the 3 months course of our study, that is in agreement with our previous findings in patients with severe conjunctivochalasis [3]. Accompanying the objective symptoms, the subjective symptoms, measured by the OSDI questionnaire also decreased during the study period. In all the cases the basal tear production was extremely low, and it did not change during the 3 months treatment. The study drug reached its goal without significant improvement in the tear secretion.

Our study shows that in cases of Sjögren's syndrome-related dry eye without serious corneal complications, the study drug used 4 times a day for three months was able to decrease the symptoms of the patients to a satisfying level.

## Conclusions

Sjögren's syndrome related dry eye may cause a chronic eye surface inflammation, in its management the use of anti-inflammatory agents might be of great importance. In our current study, we suggest the use of a special artificial tear, with a unique composition of isotonic glycerol. The isotonic glycerol has showed in vitro anti-inflammatory effect that was confirmed in our previous and present trial. Our self-controlled result showed, that in mild to moderate dry eye the use of isotonic glycerol may significantly improve dry eye symptoms substitute the use of traditional anti-inflammatory eye drops.

## Supporting Information

S1 TREND Checklist. TREND checklist. TREND Statement Checklist for the trial (PDF).

S1 Protocol. Study protocol. Study protocol for the examination of the efficiency of Conheal sodium-hyaluronate containing eye drops in conjunctival and corneal epithelial injuries as approved by the Hungarian Scientific and Research-Ethics Committee (permission No. 265/2015) and by ISRCTN database (registration number: ISRCTN17717813 (PDF).

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## Authors Contribution

Conceived and designed the experiments: JN HJK. Enrolled the patients: HJK ZZN ÁF. Performed the experiments: HJK LD. Analyzed the data: HJK. Wrote the paper: JN HJK ZZN ÁF.

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