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ORIGINAL RESEARCH

Corneal Staining Reductions Observed after Treatment with Systane® Lubricant Eye Drops

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ABSTRACT

***Introduction*:** Because of the added emphasis on ocular surface damage included in the Dry Eye Workshop's revised definition of dry eye, an evaluation of corneal staining reductions was conducted for propylene glycol/polyethylene glycol 400-based artificial tear drops (Systane® Lubricant Eye Drops; Alcon Laboratories, Fort Worth, TX, USA).

***Methods*:** An analysis was conducted on the percent change from baseline in mean corneal staining scores as reported in two previously published, randomized, double-masked, 6-week clinical studies of Systane. A descriptive comparison was also made between the outcome of the composite analysis and data obtained for Optive™ Lubricant Eye Drops (Allergan, Inc., Irvine, CA, USA). Finally, results were reviewed for an open-label study that investigated corneal staining over a 5-week period after patients discontinued Systane therapy.

***Results*:** The composite analysis included 107 Systane-treated patients. The results showed that Systane consistently reduced corneal staining at each visit; the percent change from baseline to day 42 (exit) was 47.1% ($P<0.0001$). After discontinuing Systane, immediate and significant increases in corneal staining were reported by 20 patients, with an overall increase from baseline to day 35 (exit) of 195.0% ($P<0.0001$).

***Conclusion*:** Evaluations of sum corneal ocular staining scores provide clinically meaningful evidence of dry eye severity, and are an important indicator of dry eye disease progression. The results of the composite analysis of two peer-reviewed studies indicate that Systane significantly reduced corneal staining ($P<0.0001$), indicating a reduction in the severity of dry eye.

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Finally, discontinuation of Systane results in a rapid increase in corneal staining that further confirms Systane's ability to maintain ocular surface health.

Keywords: dry eye; inflammation; ocular staining; ocular surface; Systane

INTRODUCTION

Dry eye (keratoconjunctivitis sicca) is an ocular condition that affects millions of Americans of varying ages, sexes, and overall physical health.[1] In fact, a review of recent epidemiological studies indicates that the prevalence is approximately 10% in individuals who are over 40 years of age and increases to nearly 15% in patients who are over 65 years;[2-6] the prevalence of the condition also increases in postmenopausal women and in patients with autoimmune diseases.[2,7] More specifically, these estimates indicate that around 20-30 million US patients suffer from early-stage dry eye and that roughly another 9 million US patients suffer from moderate to severe dry eye.[5]

Dry eye results from both an inadequate quantity of tear film and a disturbance of tear film stability.[8] Unlike many conditions wherein the associated signs and symptoms generally manifest in fixed combination, patients who suffer from dry eye may or may not exhibit symptoms that include dryness, burning, photophobia, foreign body sensations, grittiness, and redness, and may or may not have signs that include rapid tear film breakup, increased osmolarity, and ocular surface staining.[9] During the early stages of dry eye, it is not uncommon for symptoms to be present without any accompanying signs. As the condition progresses, however, the ocular surface damage becomes more significant even though the symptoms may lessen.[10]

In 1995, the National Eye Institute (NEI)/Industry Dry Eye Workshop published a definition of dry eye that stated, "Dry eye is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort."[11] In 2007, the International Dry Eye Workshop's (DEWS) Subcommittee for Definition and Classification revised this definition to state, "Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[10] This new definition not only recognizes the effect of dry eye on visual function, but also adds a new emphasis to the roles of hyperosmolarity of the tear film and inflammation of the ocular surface.

Current common management and therapy of dry eye includes the use of lubricants (so-called "artificial tears"), anti-inflammatory therapies, biological tear substitutes, and systemic use of antioxidants (omega-3 fatty acids).[12] It should be noted, of course, that effective manage-

ment also includes consideration of environmental factors (eg, dry climates and/or high-altitude locations) and control of potentially disruptive concomitant medications (eg, antihistamines and antidepressants that are known to increase systemic dryness).[1]

Recent increases in knowledge and understanding of the pathogenesis of dry eye have led to the development of an improved generation of artificial tear preparations that are intended to address not only tear film disorder but also disruptions of the ocular surface itself. Systane® Lubricant Eye Drops (Alcon Laboratories, Fort Worth, TX, USA) represent an improvement in artificial tear technologies. Specifically, Systane is a polyethylene glycol 400/propylene glycol-based tear that contains HP-guar as a gelling agent. Systane was developed to improve tear film stability resulting in less ocular surface staining (assessed via rose bengal, lissamine green, or fluorescein dyes; reduced staining indicates reduced ocular surface damage associated with less-severe dry eye).[9] Systane is theorized to work by binding to damaged hydrophobic areas of epithelial cells followed by attachment of a protective gel matrix intended to restore ocular surface health.[13] Thus, Systane appears clinically to have a biphasic mechanism of action that initially coats and adds volume to the tear film (bulking phase), and then restructures the film to provide long-lasting protection (tear sustaining phase).[9] Clinical studies have demonstrated the ability of Systane to significantly reduce both the signs and symptoms of dry eye relative to baseline as well as to active controls.[9,13] Studies of the ocular surface retention properties of Systane have also been reported,[9,14,15] as has its utility in dry eye treatment when paired with cyclosporine ophthalmic emulsion, 0.05% (Restasis®; Allergan, Inc., Irvine, CA, USA).[16]

As was stated previously, the DEWS Subcommittee's revised definition of dry eye adds emphasis to the condition's effect on ocular surface degradation. Given the importance of surface damage in dry eye, effective management of the condition must include a clinically meaningful reduction in staining. To that end, the purpose of this paper is to report results of a composite analysis of corneal staining based on two previously conducted studies of Systane. Additionally, in order to provide a more comprehensive evaluation of Systane's effect on corneal staining, the results of a study that investigated the impact of Systane therapy cessation will be discussed.

MATERIALS AND METHODS

Three separate clinical trials conducted in patients who used Systane have been published in the peer-reviewed literature.[13,16,17] Two of these three trials[13,16] used randomized, double-masked, parallel-group designs to compare changes in corneal staining to baseline with four-times-daily (q.i.d.) dosing. The third study[17] was an open-label evaluation of the effect on corneal staining after current Systane users discontinued therapy. All three studies were conducted in compliance with Good Clinical Practice and the ethical principles described within the Declaration of Helsinki.

In Studies 1 and 2, patients were required to have a corneal staining score of 3 or greater at both the screening (Visit 0) and eligibility visits (Visit 1). Staining was evaluated using the NEI staining grid in which a score of 0-3 is assigned to each of five corneal regions (nasal, central, temporal, superior, and inferior); a maximum combined score of 15 is therefore possible in each eye. Eligible patients also had to respond to a questionnaire indicating that their dry eye conditions necessitated treatment with artificial tears at least "some of the time." Patients who met the eligibility requirements in these two studies were randomized to treatment. Eligible patients received either Systane or a control therapy (Refresh Tears®; Allergan) q.i.d. for 6 weeks. Study 1 included 87 patients and Study 2 included 20. Over the course of 6 weeks of therapy, staining was evaluated each week and a comparison was made for the mean change from baseline to day 42 in the sum of the corneal staining scores by eye.

Study 3 included 20 patients who were currently using Systane to treat their dry eye conditions. All 20 patients discontinued therapy and entered the trial. Corneal staining was evaluated using the NEI scale on a weekly basis for 5 weeks. A comparison was made using a one-sample *t* test for the mean change from baseline to day 35 in the sum of the corneal staining scores by eye; imputations for missing data were made by carrying the last observation forward.

To evaluate more fully the effect of Systane on the ocular surface, mean corneal staining scores at each visit as reported in Studies 1 and 2 were combined statistically and, at day 42, were evaluated as a change from baseline (the "composite analysis"). A one-sample *t* test was used for the comparison. The results for Study 3 were considered independently from the composite analysis but were evaluated as a further indication of Systane's ocular surface effect.

RESULTS

The results of the individual studies have been described previously.[13,16,17] Overall, Study 1 demonstrated a reduction in corneal staining of 52.0% after 6 weeks of treatment with Systane, while Study 2 demonstrated a reduction of 35.2% after the same time period. The changes from baseline to day 42 in the sum of corneal staining scores were statistically significant in both studies ($P<0.0001$); the mean sum staining scores were 5.0 and 5.4 in Studies 1 and 2, respectively.

The composite analysis of the results from Studies 1 and 2 included 107 patients and showed a decrease in corneal staining after just 1 week of therapy that continued throughout the duration of the trial. By day 42, the composite reduction in corneal staining from baseline for Systane was 47.1%; this reduction was statistically significant ($P<0.0001$) (Figure 1).

Study 3 showed that 5 weeks after discontinuing treatment with Systane, the mean sum of corneal staining scores increased by 195.0%. The mean change from baseline in corneal staining was significant ($P<0.0001$) (Figure 2). (Note that patients in Study 3 used Systane an average of 2.1 times per day for approximately 1 year prior to entering the study and discontinuing therapy.)

Figure 1. Changes from baseline in the mean sum of corneal staining scores in Studies 1, 2, and the composite analysis for Systane. *At day 42, the reduction in staining was 52.0%, 35.2%, and 47.1% for Studies 1, 2, and the composite analysis, respectively ($P<0.0001$ for each data point relative to baseline). Study 1 included 87 patients, Study 2 included 20 patients, and the composite analysis included 107 patients. The mean baseline values were 4.9 (Study 1), 5.4 (Study 2), and 5.1 (composite analysis).

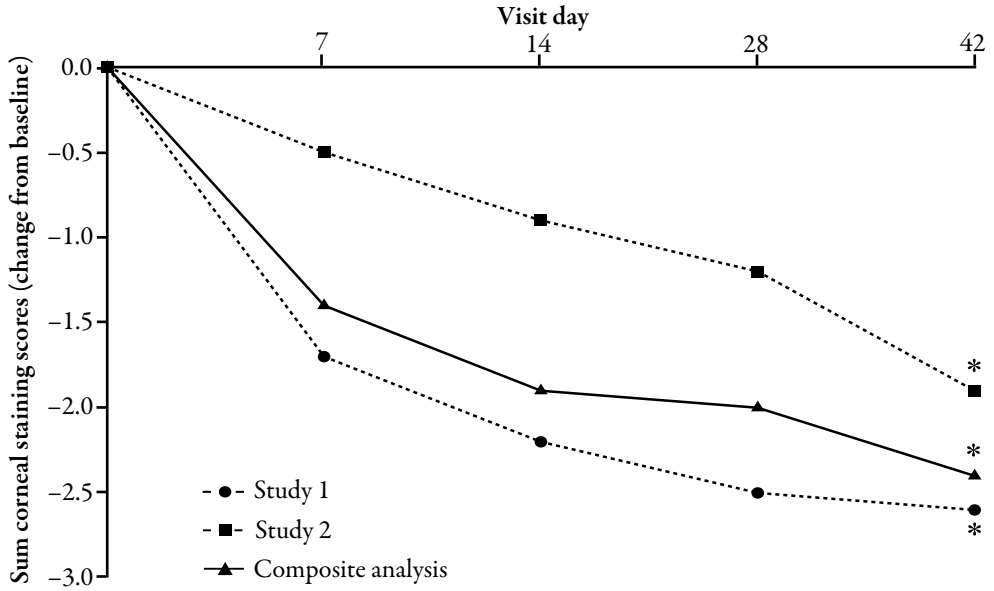
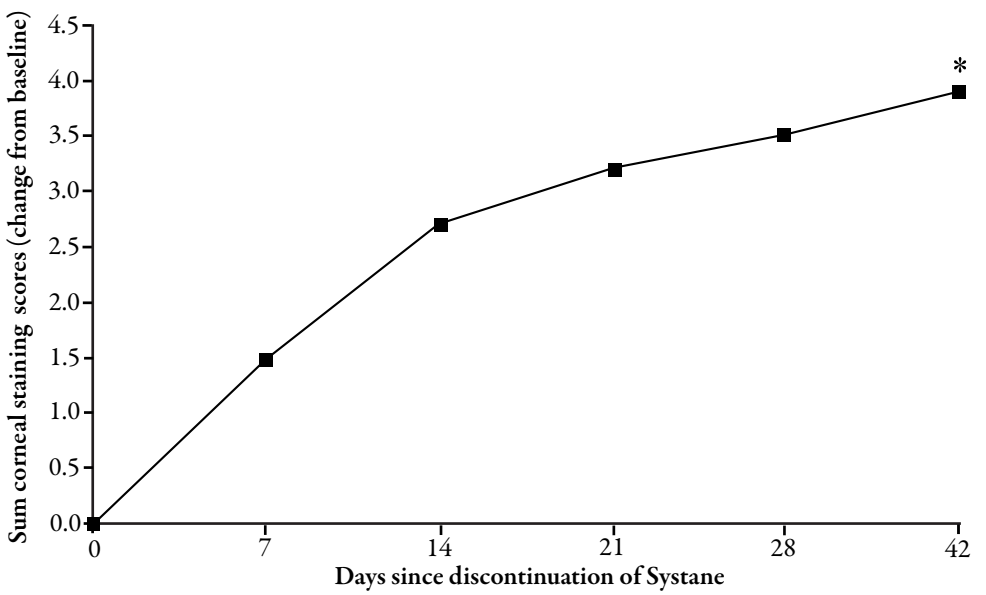


Figure 2. Change from baseline in the mean sum of corneal staining scores after discontinuation of Systane therapy. *At day 35, the increase in ocular staining relative to baseline was 195.0% ($n=20$, $P<0.0001$). The mean baseline value was 2.0.



DISCUSSION

Systane has been shown to reduce corneal staining in two separate, randomized, double-masked, parallel-group studies. Furthermore, a composite analysis of these studies indicates that Systane can significantly reduce corneal staining by as much as 47.1% in 6 weeks ($P<0.0001$). The results of a third study indicate that discontinuation of Systane leads to an immediate (within 7 days) deterioration of the corneal surface leading to a significant increase in corneal staining (195.0%) after 5 weeks ($P<0.0001$). These studies, when taken together, demonstrate the ability of Systane to impact the integrity of the ocular surface in a clinically meaningful manner.

The recent revision to the definition of dry eye was intended to emphasize that dry eye is a multifactorial condition comprised not only of tear film degradation, but also of damage to the ocular surface. In accordance with this revised definition, the DEWS report on diagnostic methodology reaffirms the importance of ocular staining and describes the three acceptable scales used in its evaluation (NEI/Industry Workshop, Oxford, and van Bijsterveld systems).[18] As the expression of dry eye is generally the same regardless of cause (host-versus-graft reaction is an exception), the DEWS report suggests that severity of the condition is more important to consider when evaluating treatment than is the condition's specific cause.[10] The DEWS report further suggests that early intervention could disrupt the core mechanism that drives dry eye[10] and thus, by extension, that an artificial tear with a demonstrated ability to restore ocular surface health may help to arrest progression of the condition. Since staining increases with increasing disease severity—conjunctival staining is often observed in the early stages, with corneal staining appearing as the condition worsens—the ability of an artificial tear to reduce staining is an important indicator of its utility in the management of dry eye.

The DEWS report includes recommendations for the design of clinical trials intended to evaluate the efficacy of dry eye therapies.[19] Specifically, the Clinical Trials Subcommittee suggested appropriate inclusion/exclusion criteria, design characteristics, assessment parameters, and analysis methodologies. With regards to the outcome parameters, the recommendations included assessments of visual acuity, tear volume and production, tear stability, tear composition, and ocular surface integrity. The Subcommittee also indicated that a combination analysis of corneal and conjunctival staining would not be appropriate and that the two evaluations should be reported separately.[19] In fact, the DEWS report states that a standardized grading system should be used to record individual area scores for each type of staining and that combined area scores for each type of staining also should be reported. While the use of fluorescein and lissamine green (or rose bengal) in ocular surface staining have certain limitations,[20-22] the Subcommittee concluded that the use of these dyes to evaluate ocular surface integrity remains the best option in clinical trials. It should be noted that, within the clinical studies described in this paper, the inclusion/exclusion criteria and study methodologies generally followed the

suggestions of the DEWS report. Similarly, the dyes used for staining (lissamine green for conjunctival staining and fluorescein for corneal staining) and the scales used to evaluate outcomes (NEI grid) complied with DEWS guidance. Finally, in these studies, outcomes for corneal and conjunctival staining were reported independently rather than solely as a composite score.

A review of the published literature provided little information to allow comparison of ocular staining results with Systane with those of other marketed artificial tear formulations. In particular, information related to Optive was sought as this product claims to be "a dual-action formula that moisturizes the surface of [the] eye while also hydrating the areas where dry eye starts."[23] As such, it is an ideal comparator for Systane. While assessments of corneal and conjunctival staining have been reported for Optive when used in combination with topical cyclosporine emulsion, 0.05%,[24] results for staining outcomes solely associated with the use of Optive are not available in the peer-reviewed literature. Results were available, however, from a slide packet used in a series of teleconferences presented by Review of Optometry.[25] The results presented in the teleconference specifically included mean corneal staining scores for Optive. Scores observed in the study for Systane and Refresh Tears, the other two included treatment groups, were not reported directly, but rather as combinations of their respective corneal and conjunctival staining outcomes. Because a combined corneal and conjunctival staining score has little clinical utility (see the previous discussion as well as the DEWS report recommendations[19]), these results do not allow for a satisfactory comparison of the three treatments.

Due to the lack of a consistently used test coupled with the fact that dry eye is a multifactorial disease with inconsistently correlated ocular signs and symptoms, the evaluation of dry eye has proven challenging.[13] Therefore, the outcomes of the studies described herein are limited by the imperfect nature of the dyes and the evaluation scales used. Furthermore, as previously stated, due to the lack of data available in the peer-reviewed literature, clear comparisons between Systane and other marketed products are not easily made and thus it is not possible to explicitly place the results of the studies conducted with Systane into a broader context.

CONCLUSIONS

The DEWS report provides a revised definition of dry eye that adds new emphasis to ocular surface degradation. Evaluations of ocular staining (corneal and conjunctival, assessed separately) provide clinically meaningful evidence of dry eye severity, with corneal staining also serving as an important indicator of disease progression. The results of the composite analysis of two peer-reviewed studies indicate that Systane significantly reduces corneal staining ($P<0.0001$), indicating an improvement in the severity of dry eye. This effect was evidenced earlier and to a greater extent than for another marketed artificial tear formulation. Finally, discontinuation of Systane results in a rapid increase in corneal staining that further confirms Systane's ability to maintain ocular surface health.

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Conflict of Interest: Dr. Christensen is an employee of Alcon Laboratories.

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