EFFICACY OF A CYCLOSPORINE-BASED DRY EYE THERAPY WITH TWO MARKETED ARTIFICIAL TEARS AS SUPPORTIVE THERAPY.

TFOS 2004

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ABSTRACT

Purpose. To evaluate the effectiveness of marketed artificial tears in relieving dry eye signs/symptoms when used as supportive therapy to a cyclosporine based ophthalmic emulsion.
Methods. 61 patients were enrolled in this randomized, investigator masked, parallel study of 6-months duration. Enrollment criteria included corneal staining of ≥ 3 (NEI grid), Schirmer w/o anesthesia of ≤ 7mm and subjects had to answer that they needed artificial tears at least "some of the time". Subjects were randomized to one of 3 treatment groups. **Treatment (Tx)1:** Restasis® (0.05% cyclosporine) BID w/Systane® (PEG 400/propylene glycol w/HP-Guar) used a minimum of 1/day as supportive therapy. **Tx2:** Restasis® BID w/Refresh Tears® (carboxymethylcellulose) used a minimum of 1/day as supportive therapy. **Tx3:** Systane alone QID. Signs and symptoms were measured at Days -7, 0, 7, 14, 28, 42, 120 and 180.
Results. A statistical difference was seen in favor of **Tx1** (Restasis+Systane) vs **Tx2** (Restasis+Refresh Tears) for corneal staining (p=0.0048) and a trend (p=0.0725) for increased TFBUT at 6 months. Schirmer showed a non-significant increase from baseline **Tx1**=1.41, **Tx2**=2.15, **Tx3**=1.42 mm. Significant differences were seen in favor **Tx1** vs **Tx2** for less Ocular Burning (p=0.0210), Stinging (p=0.0314), Grittiness (p=0.0128) and Dryness (p=0.0132). **Tx3** was better than **Tx2** for less Burning (p=0.0288), Dryness (p=0.0480) and Scratchiness (p=0.0294). Both supportive therapies were compatible with Restasis.
Conclusion. The choice of artificial tears used as supportive therapy with Restasis is important. There were significant clinical advantages with Restasis+Systane vs Restasis+Refresh Tears. While there were no clinical differences noted for Restasis+Systane vs Systane, Systane should be studied with more patients as a first line therapy. This study was sponsored and conducted by Alcon Research Ltd, Fort Worth, TX USA.

INTRODUCTION

In the prescription drug category, Restasis® Ophthalmic Emulsion (Allergan Inc. Irvine, CA) is specifically indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (KCS). In clinical trials, Restasis demonstrated statistically significant increases in Schirmer wetting of 10 mm versus vehicle at six months in these patients. This effect was seen in approximately 15% of Restasis treated patients versus approximately 5% of vehicle. Restasis is non-preserved and is packaged in unit dose vials. The active ingredient is cyclosporine (0.05%) with glycerin, castor oil, polysorbate 80, carbomer 1342 and purified water as inactives. The package insert indicates that Restasis can be used concomitantly with artificial tears allowing a 15 minute interval between products.

Systane® (Alcon) and Refresh Tears® (Allergan) Lubricant Eye Drops are both marketed under the FDA drug monograph as over-the-counter Lubricant Eye Drops. Systane contains polyethylene glycol and propylene glycol as actives and HP-guar as a gelling agent. Refresh Tears contains carboxymethylcellulose sodium 0.5% as the active demulcent. Clinical studies have shown statistically significant reductions in both signs and symptoms in mild to moderate dry eye patients in favor of Systane[1] versus Refresh Tears and significant increases in tear film break-up time (TFBUT) vs Refresh Tears through 20 minutes and through 30 minutes when compared to Refresh Endura.[2]

The purpose of this study was to evaluate the safety, efficacy and compatibility of these two marketed artificial tears (Systane and Refresh Tears) when used as concomitant therapy with Restasis Ophthalmic Emulsion in aqueous deficient patients with corneal staining.

METHODS

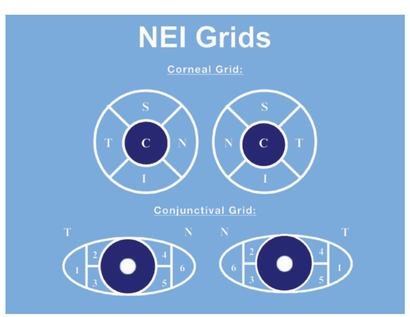
This was a six-month concurrently controlled, randomized, investigator masked, multi-site clinical study. The study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. An IRB approved this study and all patients provided written informed consent. Masking was maintained by relabeling all bottles and only the study coordinator interacted with study patients concerning product use and compliance. Sixty-one adult volunteers who signed informed consents and had a diagnosis of dry eye were enrolled at seven clinical sites, 60 were evaluable by intent-to-treat analysis. To be eligible for enrollment, patients had to express a desire to use eye drops and demonstrate sodium fluorescein corneal staining score ≥ 3 (NEI grid; 15 points possible) at the screening visit (Day -7) in one eye and again at the eligibility visits (Day 0) in the same eye. In addition patients must have demonstrated ≤ 7 mm Schirmer 1 without anesthesia at the screening visit (Day -7).

All patients who qualified at the screening visit (Day -7) were dispensed relabeled Sensitive Eyes Rewetting Drops (Bausch and Lomb, Rochester, NY), an aqueous saline solution without polymers, for use in both eyes four times per day for one week. On Day 0 (baseline), if still eligible (sum corneal staining ≥ 3 in the same eye), patients were randomized (1:1:1) to one of three treatment regimens resulting in 20 patients per group.

Regimen 1: Restasis+Systane: Restasis dosed two times per day (BID) per package instructions and Systane dosed a minimum of 1 time/day as concomitant therapy (minimum 15 minutes between drops).
Regimen 2: Restasis+Refresh: Restasis dosed BID and Refresh Tears dosed a minimum of 1 time/day as concomitant therapy (minimum 15 minutes between drops).
Regimen 3: Systane: Systane used alone dosed a minimum of four times a day.

An Eppendorf Pipette was used to instill 5 mL of non-preserved 2% sodium fluorescein (NaFI) into each eye. TFBUT was immediately measured followed by an evaluation of corneal staining, using the NEI scale (Figure 1), within 4-5 minutes. The sum of the 5 areas is reported as a composite score. Conjunctival staining was assessed by applying a Lissamine Green Strip moistened with non-preserved saline to the bulbar conjunctiva of both eyes. The degree of conjunctival staining was determined 2-3 minutes later using the NEI grid for conjunctival staining (6 areas; 0-3 scale; 18 points possible) (Figure 1). The sum of the 6 areas is reported as a composite score. Conjunctival Injection was assessed at each visit prior to instillation of any vital dyes or ocular manipulation (i.e. Schirmer test). The Schirmer 1 test (without anesthesia) was taken at Day -7, Day 42 and at the 6-month visit.

Figure 1: NEI corneal and conjunctival grids



A 5 point Ocular Comfort Frequency scale (0-none to 4-continuously) was used to assess burning, stinging, dryness, grittiness, scratchiness and foreign body sensation as felt by the patient over the previous three days prior to each visit.

Last observation carried forward was used to impute data for missed visits and discontinued patients in the intent-to-treat dataset. Baseline differences between treatment groups were evaluated with two-sided, two-sample t-tests or Chi-Square/Fisher tests as applicable. Efficacy variables were evaluated with a repeated measures analysis of variance. Least squares means comparisons were used to investigate treatment differences at each day. The type 1 error rate was set to 0.05, and 0.05<p-value<0.10 indicated a trend toward statistical significance.

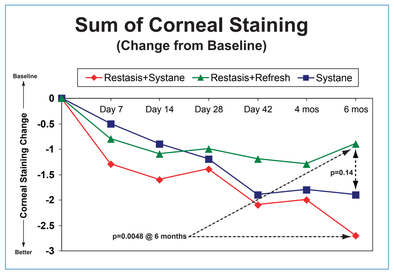
RESULTS

Average age of the study population was 59.5 years, and 80.3% of the patients were female. Baseline values for all signs and symptoms were similar. All regimens tested were safe and well tolerated by dry eye patients. No serious adverse events were reported.

Signs:

Restasis+Systane showed significantly greater total corneal staining (sum score) change from baseline than Restasis+Refresh (p=0.0048) at the six month visit (Figure 2). Systane alone, although numerically lower, was not significantly different than Restasis+Refresh (p=0.1414) for total corneal staining (sum score) change from baseline at 6 months.

Figure 2: Total corneal change from baseline in worse eye.



There was a trend for increased TFBUT at 6 months (p=0.0725) for patients in the Restasis+Systane treatment group versus Restasis+Refresh group. No statistically significant treatment differences were seen in the Schirmer Score change from baseline at 6 months (Restasis+Systane = 1.41 mm, Restasis+Refresh = 2.15 mm, Systane alone = 1.42 mm).

Symptoms:

Results of ocular symptom frequency scales of burning, stinging, grittiness, dryness and scratchiness are illustrated in Figures 3-7. Overall, Restasis+Systane was statistically significantly better at reducing dry eye symptoms compared to Restasis+Refresh. This is evidenced by less frequent burning (p=0.0210), stinging (p=0.0314), grittiness (p=0.0128) and dryness (p=0.0132) with a trend for less frequent scratchiness (p=0.0700). Systane alone showed statistically significantly less frequent burning (p=0.0288), dryness (p=0.0480) and scratchiness (p=0.0294) and trends for less frequent stinging (p=0.0605) and grittiness (p=0.0737) than Restasis+Refresh. No statistically significant differences in symptoms wre observed between Restasis + Systane and Systane alone. No treatment differences were observed for foreign body sensation.

Figure 3: Subject assessment of ocular discomfort (Burning) by visit

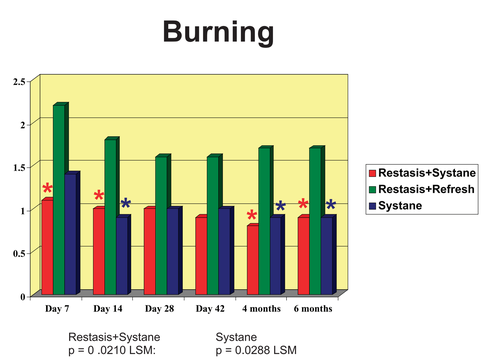


Figure 4: Subject assessment of ocular discomfort (Stinging) by visit

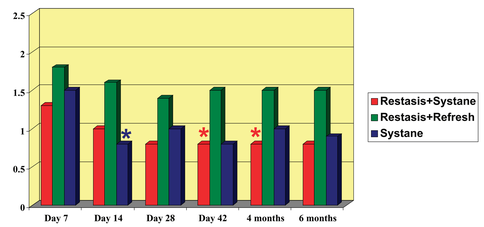


Figure 5: Subject assessment of ocular discomfort (Grittiness) by visit

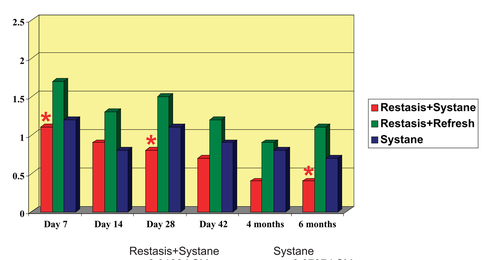


Figure 6: Subject assessment of ocular discomfort (Dryness) by visit

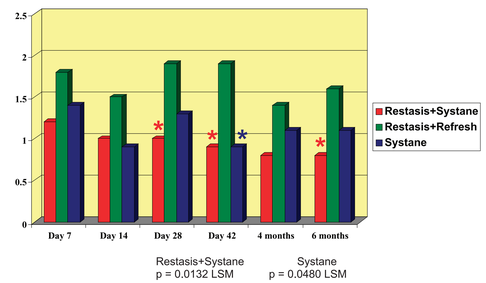
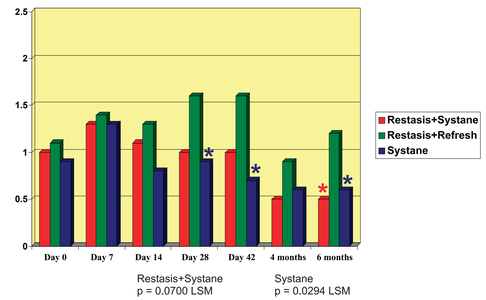


Figure 7: Subjective assessment of ocular discomfort (Scratchiness) by visit



DISCUSSION

The main objective of this study was to demonstrate compatibility of Systane® Lubricant Eye Drops when used with Restasis® Ophthalmic Emulsion. The results of this study not only showed that Systane was compatible as a concomitant tear therapy when used with Restasis, but that the combination of Restasis+Systane was statistically significantly better in reducing both the signs and symptoms of dry eye versus the combination of Restasis+Refresh Tears. Furthermore, Systane used alone was not statistically significantly different than Restasis+Systane.

Conclusions:

- Systane is compatible for use with Restasis
- The choice of concomitant medications used with Restasis has significant indications for signs and symptoms outcome measures.
- The combination of Restasis+Systane was superior to the Restasis+Refresh Tears treatment arm.

REFERENCES

1 Christensen MT, Cohen S, et al. Clinical evaluation of an HP-guar gellable lubricant eye drop for the relief of dryness of the eye. Current Eye Research 2004; 28(1):55-62.
2 Christensen M, Stein J, et. al. Evaluation of Tear Film Break-up Time Extensions by Artificial Tears in Dry Eye Patients. Abst. Opt. Vis. Sci 2003; 80(21s):106.