Efficacy and Safety of Topical 0.05% Cyclosporine Eye Drops in the Treatment of Dry Eye Syndrome: A Systematic Review and Meta-analysis

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ABSTRACT A systematic review was performed to evaluate the safety and efficacy of topical 0.05% cyclosporine in treating patients with dry eye syndrome (DES). Twelve qualified randomized-controlled trials incorporating 1367 patients were analyzed. In comparison to controls, patients who were on topical 0.05% cyclosporine eye drops had lower Ocular Surface Disease Index scores (mean difference [MD]=4.10, 95% CI: 0.25-7.96, P=.04), longer tear film breakup time (MD=2.30 seconds, 95% CI: 0.75-3.86, P=.004), improved Schirmer I scores (MD=2.77 mm/5min, 95% CI: 1.63-3.91, P=.00001), reduced corneal fluorescein staining (standardized mean difference [SMD]=0.61, 95% CI: 0.07-1.15, P=.03), and higher goblet cell densities (SMD=1.68, 95% CI: 0.54-2.81, P=.004). However, there were more adverse effects in the cyclosporine patient group (odds ratio=1.64, 95% CI: 1.17-2.30, P=.004). Topical 0.05% cyclosporine eye drops twice daily significantly improved both the objective and subjective outcomes in DES patients. The study limitations in the clinical, methodological and statistical heterogeneities are discussed.

KEY WORDS cornea, cyclosporine, dry eye syndrome, keratoconjunctivitis sicca, meta-analysis, ocular surface, systematic review

I. INTRODUCTION

Dry eye syndrome (**DES**) is a multifactorial disease of the ocular surface with tear film abnormalities, leading to eye discomfort, visual disturbance, tear film instability, and inflammation of the ocular surface.[1] DES accounts for as many as 17%-25% of visits to ophthalmology clinics,[2,3] making it one of the most common ocular conditions.[4,5] Patients with uncontrolled and chronic DES are at risk for ocular infections[6,7]; however, due to the natural defense mechanisms of the eye, overt intraocular infections are relatively uncommon.[8,9]

The understanding of DES pathogenesis has advanced from the simple concepts of deficiency or impaired quality of tears, and now includes concepts of tear hyperosmolarity and ocular surface inflammation. Reduced tear production and/or increased tear evaporation results in tear hyperosmolarity, which, in turn, leads to T lymphocyte-mediated release of inflammatory mediators.[10-13] As the surface epithelium is damaged by these mediators, a secondary reduction in mucin production further exacerbates tear film instability.[14] Inflammation is also a contributing factor to evaporative loss. The accumulation of meibum within the meibomian glands causes inflammation and bacterial colonization.[14,15] The normal composition of meibum is altered by the lipase from these bacteria.[16] As a result, polar lipids diffuse more easily through the aqueous layer, leading to tear film instability.[17] Furthermore, as the abnormal meibum solidifies, the accumulation of meibum obstructs the ducts, perpetuating the vicious cycle of inflammation and evaporative tear loss.

Traditional therapies for DES mainly focus on the lubrication of the ocular surface with artificial tears. However, these treatments do not address the underlying ocular

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surface inflammation. Cyclosporine, an immunomodulatory agent, has been shown to block T-cell proliferation and receptor signal transduction. The cell-mediated inflammatory responses are modulated through the downregulation of IL-2 receptor expression and gene transcription.[18-21] Because of the properties noted above, topical cyclosporine eye drops are indicated for the treatment of DES. Commercial topical 0.05% cyclosporine (Restasis; Allergan, Inc., Irvine, CA) has been approved by the U.S. Food and Drug Administration (**FDA**) for the treatment of dry eyes since April 2003. A number of clinical trials had been conducted to evaluate the safety and effectiveness of topical 0.05% cyclosporine since its launch. However, the results were inconsistent, and we therefore set out to conduct a systematic review and meta-analysis to examine the clinical evidence of topical 0.05% cyclosporine in the treatment of DES.

II. METHODS

A. Search Strategy

We performed our search with MEDLINE and EMBASE via the OVID platform, Cochrane Central Register of Controlled Trials (**CENTRAL**), ClinicalTrials.gov (www.clinicaltrials.gov), and World Health Organization International Clinical Trials Registry Platform (**WHO ICTRP**) for randomized controlled trials (**RCTs**) that evaluated topical 0.05% cyclosporine eye drops versus controls for DES. We used the Cochrane highly sensitive search strategy[22] in combination with our search terms as listed in Appendix 1. We then manually searched the references of all relevant articles to identify any potential missing studies not found by electronic means. We did not apply any language restrictions. The final search was performed on July 4, 2013 for all of the databases.

B. Inclusion and Exclusion Criteria

RCTs were eligible for inclusion if the following criteria were satisfied:

1. Patients having a diagnosis of DES prior to the study, defined as:
   A. Schirmer score, with or without anesthesia, >0 mm/5min and ≤ 10 mm/5min; or
   B. Tear film break-up time (**TFBUT**) ≤ 10 seconds; or
   C. Presence of superficial punctate keratitis as evidenced by corneal fluorescein staining on slit-lamp examination; or
   D. Total corneal fluorescein staining score of ≥ 4 (National Eye Institute Industry/Workshop Scale[23]); or
   E. Score of ≥ 3 (0-6 scale) on 4 of the 16 questions of the Ocular Comfort Index (**OCI**[24]); or
   F. Score of ≥ 22 for the Ocular Surface Disease Index (**OSDI**[25]); or
   G. Positive for symptoms of tear film instability associated with DES, such as dryness, irritation, photophobia, tearing and foreign body sensation.
2. Patients were subjected to topical 0.05% cyclosporine eye drops twice daily;
3. Treatment with topical 0.05% cyclosporine eye drops was compared head-to-head with artificial tears, placebo (vehicle), or no topical treatment.
4. As there is no single gold standard diagnostic test for DES, and the signs and symptoms of DES are often poorly correlated,[26] we included any RCTs that examine at least one of the following outcomes: OSDI, corneal fluorescein staining, TFBUT, Schirmer test with and without anesthesia, goblet cell density and occurrence of any ocular and systemic treatment-related adverse effects.

Studies were excluded based on the following criteria:

1. Patients had a history of topical or oral cyclosporine use within the past one year; and/or
2. Patients had a history of previous or concurrent use of other topical and/or oral treatments that may interfere with the outcomes; and/or
3. RCTs where the prime objective of treatment was not directly related to dry eyes, but rather having dry eyes as a manifestation of the syndrome or condition studied; and/or
4. Outcomes or data presented in a format that cannot be extracted for analysis (i.e., no corresponding standard deviation was provided along with the outcome measurement or data presented in a qualitative manner).

C. Data Extraction

We extracted data from studies that fulfilled the inclusion and exclusion criteria. We used a standardized form to record data on the authors of the study, year of publication, country of study, etiology of DES, type of intervention used as control, sample size, mean age, gender, duration of follow-up, and outcome measures. Outcomes in the change-