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Title: Efficacy and safety of nanomicellar cyclosporin 0.09% in patients with dry eye disease refractory to emulsion cyclosporin 0.05%: a prospective crossover study

Abstract body:

Purpose: Emulsion 0.05% cyclosporin (commercially, and, herein, Restasis), remains central to the management of dry eye disease (DED). Within the ocular surface microenvironment, cyclosporin inhibits transcription factors governing pro-inflammatory cytokines and prevents T cell activation, thereby reducing inflammation and restoring tear film homeostasis. Despite considerable evidence supporting the efficacy of Restasis, some patients continue to be symptomatic while receiving treatment. In such cases, inadequate delivery of cyclosporin to the ocular surface is posited to be the underlying mechanism for treatment failure. As cyclosporin is a hydrophobic molecule, and in Restasis and generics, packaged in a hydrophobic emulsion vehicle, delivery to the hydrophilic aqueous environment of the ocular surface is inherently limited. Recently, Health Canada approved a novel formulation of cyclosporin for treatment of DED. This preparation (commercially, and, herein, Cequa) contains 0.09% cyclosporin, packaged in a nanomicellar vehicle with hydrophilic properties. It is posited that this hydrophilic vehicle coupled with the increased concentration of cyclosporin may better address ocular surface inflammation. The purpose of this study is to evaluate the efficacy and safety of Cequa for treatment of DED in patients with partial or no response to Restasis.

Study Design: Prospective crossover study

Methods: Our study was conducted in adherence with the principles of the Declaration of Helsinki, and we received institutional research ethics board approval. We enrolled adult patients with a diagnosis of moderate-to-severe DED (ocular surface disease index; OSDI ≥22) with partial or no amelioration of symptoms following at least six-months of treatment with Restasis. Our primary outcome was the corneal inter-palpebral conjunctival staining score as defined in the Oxford Scheme 6-point scale. Secondary outcomes were: tear break-up time (TBUT, in seconds), Schirmer strip test (in millimeters), OSDI score, and adverse events as reported by patients. All outcomes

were assessed at baseline as well as at day 42 and day 84 after commencing treatment with Cequa. Our analyses were summarized using repeated measures analysis of variance.

Results: We enrolled 7 patients (14 eyes). The mean Oxford staining score decreased significantly from 1.50 at baseline to 0.30 by the end of the study ($p<0.05$) and the TBUT increased significantly from 3.8s to 4.8s ($p<0.05$). Schirmer tear testing trended towards an increase from 12.0mm at baseline to 15.3mm at day 84 ($p=0.10$) and the OSDI decreased from 44.2 at baseline to 38.3 at the end of the study period ($p=0.91$). No significant adverse events were reported by patients.

Conclusions: Nanomicellar 0.09% cyclosporin has utility in the management of DED recalcitrant to treatment with emulsion 0.05% cyclosporin.