Evaluation of a cyclosporine A ophthalmic ointment in an experimental mouse model of dry eye.

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Introduction

Dry eye is a common disease with multifactorial causes. Symptoms typically include irritation, dryness, burning and decreased or fluctuating vision. It is recognized that inflammation with innate and adaptative immunity has a key role in the pathogenesis. Anti-inflammatory drugs are widely used for the treatment of the inflammation produced by the disease with corticoids or cyclosporine A (CsA). Restasis® (Allergan), a CsA emulsion, was approved by the FDA but is not available in Europe. Here we propose to show the action of Optimmune® (MSD Animal Health) a marketed veterinary ophthalmic ointment that contains CsA in an experimental mouse model of dry eye induced in a controlled environmental room by scopolamine, a tropane alkaloid drug with muscarinic antagonist effects.

Materials and methods

Animals:

For this model, thirty female C57BL/6N mice (20g) were randomized in three groups of ten animals: a naïve group (not induced) and two induced groups, one treated by topical ocular administration of ophthalmic ointment that contains 0.2% CsA and the other one by topical ocular administration of vehicle three times daily (T.i.d.). Experimental dry eye was induced by applying a transdermal scopolamine patch (0.5mg/72h, Scopoderm® TTS, Novartis) on mice that were placed in a controlled environmental room (CER) (relative humidity <25%, air-flow 15l/min, temperature 20-22°C and 12h:12h light-dark cycle (10-200 lux) from D1 to D14). All efforts were made to minimize suffering of the mice and all experiments were performed according to the internal ethics committee. Food and water were available ad libitum.

Clinical Evaluations:

Tear production was measured with a cotton thread test (Zone Quick, FCI Ophthalmics, USA) in the lateral canthus of the conjunctival fornix for 30 seconds.

Corneal defects were examined by slit-lamp observation using blue light after instillation of 0.5μl of 0.5% sodium fluorescein. Punctate staining was measured using a grading system (National Eye Institute) giving a 0-3 score to each of 5 areas of a divided cornea for a maximum score of 15°.

Results

These examinations were performed in both eyes in the mice at baseline and on D3, D7 and D14.

Cotton Thread Test:

The mice housed in the CER and exposed to scopolamine showed a rapid and significant decrease of lacrimation by D3. Topical ocular administration of cyclosporine A showed a significant increase of the tear volumes on D14.

Fluorescein Staining

Fluorescein staining was measured using a grading system (National Eye Institute) giving a 0-3 score to each of 5 areas of a divided cornea for a maximum score of 15°.

References


Conclusion

Inflammation has a key role in the pathogenesis of the dry eye syndrome. It is the cause and the consequence of dry eye. The action of cyclosporine A in this disease has been known since 1989 in animals affected with spontaneous keratoconjunctivitis sicca. Now cyclosporine is considered as a standard treatment for dry eye syndrome. In our experimental mouse model of dry eye, cyclosporine A leads to an increase of lacrimation and a reduction of corneal damage. This model with simple experimental handling and low cost, can be used as a tool for discovering therapeutic drugs in dry eye disease targeting the inflammation, tear secretion and cornea defect.