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Clinical evaluation of pimecrolimus eye drops for treatment of canine keratoconjunctivitis sicca: A comparison with cyclosporine A

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Abstract

The aim of this study was to evaluate the efficacy of pimecrolimus oil-based eye drops in alleviating the clinical signs of keratoconjunctivitis sicca (KCS) in dogs and to compare the efficacy with that of cyclosporine A (CsA) ointment. An open-label, multicenter study enrolling 44 dogs previously untreated with CsA was conducted. Dogs were randomly assigned to a treatment group and medicated twice daily for 8 weeks. After that time the mean increase (±SEM) in the Schirmer tear test was 9.2 ± 1.6 mm/min in the pimecrolimus group and 5.8 ± 1.1 mm/min in the CsA group ($P = 0.085$). The improvement in clinical signs of inflammation in eyes treated with pimecrolimus was significantly greater than in eyes treated with CsA ($P = 0.02$). The results show that 1% pimecrolimus oily eye drops are as safe as and more effective than CsA ointment in controlling KCS in dogs.

Keywords: Dog; Keratoconjunctivitis sicca; Dry eye; Cyclosporine A; Pimecrolimus

Introduction

Tears play an important role in maintaining the health and normal function of the cornea and conjunctiva; they provide essential nutrients to the cornea, help remove foreign matter and waste products, and contain immunoglobulins, lysozymes and other components of the ocular defense mechanisms. Therefore, it is not surprising that tear deficiency is a major cause of corneal and conjunctival inflammation. Millions of people worldwide are afflicted with keratoconjunctivitis sicca (KCS), or dry eye, and symptoms of the disease are reported by 17–25% of patients visiting ophthalmic clinics (McCarty et al., 1998; Moss et al., 2000; Schaumberg et al., 2003). The disease is also prevalent in dogs, with a diagnosis of KCS made in 1–1.5% of all dogs visiting veterinary teaching hospitals in North America (Kaswan et al., 1991; Helper, 1996).

In both humans and dogs, the most common form of dry eye is a quantitative deficiency in the middle, aqueous layer of the tear film. This deficiency can cause a large range of clinical signs, depending on the severity and duration of the disease. Acute cases may present with severe pain and corneal ulceration which may rapidly progress to corneal perforation and iris prolapse (Moore, 1999). Chronic cases present with classic signs of keratitis (including infiltration of inflammatory cells, vascularization, pigmentation and thickening) and conjunctivitis (including

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congestion, pigmentation and thickening) (Moore, 1999). Mucoid to mucopurulent discharge is present, and secondary bacterial infection is a common complication. Visual acuity is affected due to loss of the contribution of tears to the overall refractive power of the eye (Montes-Mico et al., 2004) and because of deterioration in corneal transparency.

There are numerous causes of KCS in the dog. The leading cause is most likely immune-mediated dacryoadenitis (Moore, 1999). Histopathological studies of lacrimal tissue of affected dogs show lymphocytic–plasmacytic infiltration associated with acinar atrophy, suggesting an immune-mediated basis for the disease in this species (Kaswan et al., 1984; Bounous et al., 1995). Circulating antibodies to the lacrimal gland and the nictitating gland have been found in significant numbers of affected dogs (Kaswan et al., 1985). The disease may also be associated with systemic canine autoimmune conditions, including systemic lupus erythematosus (SLE), rheumatoid arthritis and pemphigus. A high percentage of dogs with KCS are also positive for rheumatoid factor (34%), antinucleolar antibodies (40%), or have high levels of gamma globulins (90%) (Kaswan et al., 1983, 1985). In humans it is also suspected that an autoimmune inflammation of the lacrimal glands, mediated by T cells, similarly plays an important role in the disease pathogenesis (Pflugfelder et al., 1986, 1999).

Further indication of the immune-mediated inflammatory etiology of the disease comes from studies in dogs and humans demonstrating that topical cyclosporine A (CsA) is an efficacious treatment for KCS. This immunosuppressive therapy results in a significant increase in tear production and improvement in clinical signs of inflammation in dogs (Olivero et al., 1991; Morgan and Abrams, 1991; Sansom et al., 1995), and for the past 15 years veterinarians have been using CsA ointment (Optimmune; Schering-Plough) or solution for treatment of canine KCS. Successful trials in humans (Sall et al., 2000; Stevenson et al., 2000) have recently led to the approval of a CsA ophthalmic emulsion (Restasis; Allergan) for the treatment of human patients.

However, a significant number of canine KCS patients do not respond to CsA treatment (Berdoulay et al., 2005), and patent and supply issues affect availability in some markets. Pimecrolimus (SDZ ASM 981; Novartis Institute for BioMedical Research) is a new ascomycin derivative which interferes selectively with the activation of T cells and mast cells and inhibits the production of inflammatory cytokines. The drug has been demonstrated to be more than 10-fold more effective than CsA in inhibiting cytokine production by T cells in vitro and has proven also to be superior to CsA in animal models of skin inflammation (Meingassner et al., 1997, 2003; Grassberger et al., 1999; Kalthoff et al., 2002). In a previous exploratory study, pimecrolimus has shown significant activity in animal models of immune-mediated inflammatory eye diseases, in particular in canine KCS (Nell et al., 2005). The aim of the present study was to conduct a large, multicenter, outpatient clinical dog trial to confirm the efficacy of topical pimecrolimus in alleviating clinical signs of KCS in dogs and compare it with the veterinary form of CsA (Optimmune).

Materials and methods

Animals

An open-label, multicenter, randomized, 8-week outpatient clinical dog study was conducted by four Diplomates of the European College of Veterinary Ophthalmologists. The study was approved by the respective Institutional Animal Care and Use Committees and all investigations adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. The dog owners read an information sheet and signed an informed consent form prior to participation.

Dogs of either gender and of any breed or age were enrolled in the study following diagnosis of uni- or bilateral KCS. KCS was diagnosed based on medical history, a Schirmer tear test (STT) value $\leqslant$10 mm/min *and* a total score $\geqslant$4 in grading clinical signs of conjunctival and/or corneal inflammation (for details see below). Dogs were excluded from the study if they had ever been treated previously with topical or systemic CsA or with any of the following drugs within 14 days before the study: topical or systemic corticosteroids, atropine, antihistamines, pilocarpine, or sulfa-containing drugs; phenazopyridine; essential fatty acids; or general anesthetics. Other exclusion criteria included the presence of any systemic disease other than dermatological disorders or of any ocular diseases affecting the ocular surface other than those related to orbital conformation in brachycephalic breeds. Dogs in which KCS was determined to be congenital, secondary to neuroparalysis, to surgery of the nictitans gland, to distemper or to the use of lacrimotoxic drugs, were not included in the trial. Cases of KCS that had undergone parotid duct transposition or lacrimal duct occlusion were also excluded.

Treatments

The test material was 1% pimecrolimus experimental corn oil-based eye drops. The 1% pimecrolimus ophthalmic formulation was sterilized by filtration, and then aseptically filled into 5 mL polypropylene bottles with polypropylene droppers and high density polyethylene closures. Storage and use conditions were also mentioned on the bottle. Stability of the formulation was guaranteed for the duration of the study, if required storage conditions were observed.

Optimmune (Schering-Plough), the commercial ophthalmic ointment approved for veterinary use containing 0.2% CsA, was used as the comparative product. In severe cases, when considered necessary by the investigator, the dogs were treated t.i.d. with commercial artificial tears (Oculotect Fluid, Novartis). In cases of corneal ulceration, topical treatment (TID) with chloramphenicol solution was also permitted. It was allowed to clean secretions from the lids 15 min prior to drug administration. When several medications were administered, the order of treatment was as follows: artificial tears, followed by chloramphenicol solution, followed by the KCS medication. Owners were instructed to wait 15 min between medications.

Dogs that met the inclusion criteria were randomly assigned to either the CsA or the pimecrolimus group. Both treatments were administered twice daily for 8 weeks in both eyes. In cases of unilateral disease, only the data of the affected eye were analyzed in this study.

Evaluation of clinical efficacy

Upon enrollment and at weeks 2, 4 and 8, all dogs underwent complete physical and ophthalmic examinations, including slit-lamp biomicroscopy, STT and indirect ophthalmoscopy. The STT was performed using commercial tear test strips from the same lot (Schering-Plough). A complete medical history was recorded at each visit, with special attention paid to