Journal of Zoo and Wildlife Medicine 37(4): 562–564, 2006

SUSTAINED RELEASE CYCLOSPORINE THERAPY FOR BILATERAL KERATOCONJUNCTIVITIS SICCA IN A RED WOLF (*CANIS RUFUS*)

Anne E. Acton, D.V.M., A. Brady Beale, V.M.D., Brian C. Gilger, M.S., D.V.M., Dipl. A.C.V.O., and Michael K. Stoskopf, D.V.M., Ph.D., Dipl. A.C.Z.M.

Abstract: A 12-yr-old intact male red wolf (*Canis rufus*) diagnosed with bilateral idiopathic dry eye was treated with subconjunctival drug delivery implants designed to release therapeutic levels of cyclosporine from 12–24 mo. Normal tear production and corneal health has been maintained, alleviating the need for daily handling of the animal for topical medication.

Key words: *Canis rufus*, cyclosporine, dry eye, keratoconjunctivitis sicca (KCS), sustained-release delivery, red wolf.

BRIEF COMMUNICATION

Keratoconjunctivitis sicca (KCS or ''dry eye'') is defined by reduced production or increased evaporation of tears that result in damage to the corneal surface. Tear film is comprised of a mucus layer produced by conjunctival goblet cells, an aqueous layer produced by the lacrimal and nicitans glands, and a superficial lipid layer produced by meibomian glands of the eyelids.[4,8] Inadequate production of any of these layers or disorders that prevent the complete closure of the eyelids disrupt the distribution of the protective tear film across the globe. If left untreated, poor lubrication can lead to chronic corneal ulceration, ocular discomfort, corneal edema, opportunistic infections, and eventual blindness.[1] In domestic dogs (*Canis lupus familiaris*), Schirmer tear test (STT) values of <5 mm/min indicate inadequate aqueous tear production, which is the most common manifestation of KCS.[2] Current medical management recommendations consist of artificial tear replacement and the stimulation of natural tear production with immunomodulating agents such as cyclosporine.[5] These topical medications require lifelong daily administration, and such frequent handling often is impractical in zoo settings. This report outlines the successful management of bilateral KCS in a captive red wolf (*Canis rufus*) using experimental, sustained-release cyclosporine subconjunctival implants.

A 12-yr-old intact male red wolf (22 kg) housed alone in an outdoor pen was noted to have focal alopecia on the scalp and around both eyes in association with recent excoriation. Closer inspection under manual restraint revealed bilateral thick, yellow-green discharge at the medial canthi. Chemosis, conjunctival vessel injection, and vascularization of the dorsal limbus of the left cornea were seen also. Both ear canals were malodorous with excessive moist, brown exudate. The initial STT revealed that tear production was 0 mm/min in both eyes (OU). No fluorescein stain uptake was noted in either eye. Cytologic examination of multiple superficial and deep skin scrapings, as well as ear swabs, revealed many gram-positive cocci and budding yeast (7–10/h.p.f.), degenerate neutrophils, and occasional macrophages. No ectoparasites or ova were seen. Initial treatment consisted of cefpodoxime proxetil (Simplicef®, Pfizer Animal Health, New York, New York 10017, USA; 150 mg p.o. s.i.d. $\times$ 3 wk) for the pyoderma and a combination ophthalmic regimen (OU s.i.d. $\times$ 2 wk) consisting of topical cyclosporine 0.2% ointment (Optimmune®, Schering-Plough Animal Health, Union, New Jersey 07083, USA) and triple antibiotic ointment with dexamethasone (Falcon Pharmaceuticals, Ltd., Ft. Worth, Texas 76134, USA) to treat the conjunctivitis and to evaluate the animal's response to cyclosporine therapy prior to surgical placement of bilateral subconjunctival drug delivery implants. The animal tolerated daily capture and manual handling for eye medications without incident.

The eyes showed marked improvement after 1 wk of daily topical therapy. Bilateral ocular discharge ceased and conjunctival injection resolved. Schirmer tear test results after 2 wk of topical ther-

From the Environmental Medicine Consortium (Acton, Gilger, Stoskopf), Department of Clinical Sciences, 4700 Hillsborough Street, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, 27606, USA; and the Ophthalmology Service (Beale, Gilger), Department of Clinical Sciences, 4700 Hillsborough Street, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, 27606, USA. Correspondence should be directed to Dr. Acton.

Figure 1. Surgical placement of a cyclosporine sustained-release implant through an incision in the dorsolateral bulbar conjunctiva. The wolf is in right lateral recumbency with the left globe rotated ventrally.

apy were 15 mm/min OS and 16 mm/min OD, which are baseline values in healthy domestic dogs.[2] Intermittent fresh excoriations associated with the dermatitis prompted the addition of ketoconazole (PLIVA, Inc., East Hanover, New Jersey 07936, USA; 100 mg p.o. s.i.d. × 3 wk) to the treatment regimen. The wolf's favorable response to topical cyclosporine supported a decision to surgically implant experimental cyclosporine delivery devices designed to slowly release therapeutic levels of the drug up to 12 mo.[3] Effective treatment intervals as long as 24 mo have been observed in beagles with these same implants (Gilger, unpubl. data).

The wolf was anesthetized with medetomidine (Domitor®, Pfizer Animal Health, Exton, Pennsylvania 19341, USA; 0.04 mg/kg i.m.) and butorphanol (Torbugesic®, Ft. Dodge Animal Health, Ft. Dodge, Iowa 50501, USA; 0.4 mg/kg i.m.) after an overnight fast. Topical proparacaine HCl ophthalmic solution, 0.5% (Falcon Pharmaceuticals, Ft. Worth, Texas 76134, USA) and topical phenylepherine HCl 2.5% (Bausch & Lomb, Inc., Tampa, Florida 33637, USA) were instilled in both eyes. The skin around the surgical site was prepared with dilute betadine solution and sterile saline. An eyelid speculum provided maximum exposure of the globe. A 2-mm incision was made into the dorsolateral bulbar conjunctiva 7 mm posterior to the limbus. Westcott scissors were used to bluntly undermine the conjunctiva medially and laterally. A gamma-irradiated cyclosporine implant (13 mm long × 3 mm diameter, 10% matrix cyclosporine/silicone) was inserted longitudinally into the subconjunctival pocket (Fig. 1). The incision was closed with a single cruciate 6-0 polygalactin suture. Total surgery time for each eye was less than 10 min. Anesthesia was reversed with atipamezole (Antisedan, Pfizer Animal Health, Exton, Pennsylvania 19341, USA; 0.2 mg/kg i.m.). Postoperative management included daily observation of the implants for suture reaction or extrusion and application of topical ophthalmic antibiotic ointment (E Fougera & Co., Melville, New York 11747, USA; OU s.i.d. × 1 wk) to reduce the risk of infection. Schirmer tear tests were repeated at regular intervals. The implants could be visualized through the conjunctiva by gently retracting the dorsal eyelid and lightly depressing the globe with the lower eyelid. All oral medications were discontinued 1 wk after surgery following resolution of the skin condition. Schirmer tear tests were repeated at regular intervals and were interpreted as normal (16 mm/min OD and 18 mm/min OS) 2 wk postoperatively. At 4 wk post-op, a small amount of dried yellow discharge was detected at the medial canthus of the left eye. The implant and suture were still clearly visible, but chemosis had returned. The right eye appeared normal. An STT yielded 9 mm/min OS and 23 mm/min OD tear production. Mild conjunctivitis was suspected, so treatment with topical antibiotic with dexamethasone (s.i.d. OS × 1 wk) was resumed, following a negative fluorescein dye test, and the ocular discharge resolved over 3–4 days. Tear production immediately following the completion of supplemental therapy returned to normal (20 mm/min OS, 16 mm/min OD) and continued in the normal range (16 mm/min OU) 1 wk later without further treatment. Twelve months after surgery, tear production remained ≥13 mm/min OU with the cyclosporine implants alone.

Most cases of KCS presumably result from an immune-mediated response characterized by lymphocytic infiltrates and fibrosis in lacrimal acini with subsequent conjunctival squamous metaplasia.[1] Immune-mediated diseases in humans have been associated with KCS, including Sjögren-like syndrome, lupus erythematosus, rheumatoid arthritis, hypothyroidism, ulcerative colitis, diabetes mellitus, glomerulonephritis, and atopy.[2] Additional etiologies for KCS in the dog include primary infections (canine distemper virus, leshmaniasis), drugs (sulfa, psychotropics, atropine, general anesthesia), neurogenic causes (facial nerve CN7, trigeminal nerve CN5), eyelid trauma, neoplasia, mucin deficiency, irradiation, surgical removal of lacrimal glands, or breed predilections.[1] Eyelid anatomy and function were within normal limits in this wolf and he was not on any medications known to decrease tear production. Severe otitis media (left

ear) was diagnosed in this animal that potentially affected the facial nerve innervation to the lacrimal gland.[1] A thyroid panel at the time of surgery was consistent with a diagnosis of a sick euthyroid syndrome in a domestic dog. This particular animal has a history of persistent eosinophilia, despite the absence of fecal or ectoparasites, which could be consistent with atopy and associated dry eye. Immune-mediated KCS is, however, the most likely diagnosis in this animal and is often a diagnosis of exclusion that can be confirmed by response to therapy.

Topical cyclosporine, a 1.2 kDa cyclic peptide, has become the treatment of choice for KCS in canine patients.[5] It is a noncytotoxic, immunomodulating drug that specifically inhibits the CD4+ T-helper cell production of certain cytokines (IL-2, IL-6, macrophage activation factor), thereby inhibiting inflammation and T-cell proliferation. Cyclosporine also inhibits rapid fibroblast and keratinocyte proliferation, while suppressing acinar and conjunctival cell apoptosis so aqueous tear and mucin production is preserved.[6] Cyclosporine increases tear production within 2–3 wk of treatment initiation, whereas its discontinuation results in decreased tear production within 12–24 hr and a recurrence of clinical signs.[1] Dogs receiving chronic topical therapy (>5 yr) do not appear to become refractory to the drug.[7]

Cyclosporine is lipophilic, making delivery of therapeutic levels to ocular tissues challenging. Systemic administration has caused toxic renal, hepatic, and gastrointestinal side effects, and topical administration often is cleared by the nasolacrimal system or conjunctival blood supply before adequate therapeutic levels can be achieved. The subconjunctival device implanted in the wolf was designed to slowly release cyclosporine locally; pharmacodynamic studies performed in dogs demonstrated that the implant released the drug at an average rate of 20 μg/day for the first month and then tapered to a steady state of 10 μg/day for at least 6 mo, with no evidence of toxicity.[3] Clinical trials in addition to the implanted wolf have shown a positive response of STT values >15 mm/min sustained once topically applied cyclosporine has been discontinued (Gilger, unpubl. data). The response to sustained release cyclosporine implants in this wolf provides encouraging documentation for a practical treatment for immune-mediated KCS in a zoo setting.

LITERATURE CITED

1. Kaswan, R. L., and M. A. Salisbury. 1990. A new perspective on canine keratoconjunctivitis sicca: treatment with ophthalmic cyclosporine. Vet. Clin. North Am. Small Anim. Pract. 20: 583–625.

2. Kaswan, R. L., M. A. Salisbury, and D. A. Ward. 1989. Spontaneous canine keratoconjunctivitis sicca. A useful model for human keratoconjunctivitis sicca: treatment with cyclosporine eye drops. Arch. Ophthalmol. 107: 1210–1216.

3. Kim, H., K. G. Csaky, B. C. Gilger, J. P. Dunn, S. S. Lee, M. Tremblay, F. de Monasterio, G. Tnasey, P. Yuan, P. M. Bungay, R. J. Lutz, and M. R. Robinson. 2005. Preclinical evaluation of a novel episceral cyclosporine implant for ocular graft-versus-host disease. Invest. Ophthalmol. Vis. Sci. 46: 655–662.

4. Lemp, M. A., and H. J. Blackman. 1983. Physiology of tears. *In:* Milder, B., and B. A. Weil (eds.). The Lacrimal System. Appleton-Century-Crofts, Norwalk, Connecticut. Pp. 49–54.

5. Moore, C. P. 2000. Keratoconjunctivitis sicca. *In:* Bonagura, J. D. (ed.). Kirk's Current Veterinary Therapy XIII: Small Animal Practice. W. B. Saunders Co., Philadelphia, Pennsylvania. Pp. 1061–1066.

6. Moore, C. P., J. B. McHugh, J. G. Thorne, and T. E. Phillips. 2001. Effect of cyclosporine on conjunctival mucin in a canine keratoconjunctivitis sicca model. Invest. Ophthalmol. Vis. Sci. 42: 653–659.

7. Morgan, R. V., and K. L. Abrahms. 1991. Topical administration of cyclosporine for treatment of keratoconjunctivitis sicca in dogs. J. Am. Vet. Med. Assoc. 199: 1043–1046.

8. Pflugfelder, S. C., A. Solomon, and M. E. Stern. 2000. The diagnosis and management of dry eye: a twenty-five-year review. Cornea. 19: 644–649.

Received for publication 18 March 2006