HOW I TREAT PERIANAL FISTULAS
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The surgical treatment of perianal fistulas has been fraught with complications and a high (generally 40-50%) recurrence rate. Recommended treatments have included cryosurgical destruction of diseased perianal tissues, electrofulguration, rectal pull-through, and caudectomy (tail amputation). Complications have included rectal stricture, recurrence, and fecal incontinence. The underlying etiology of perianal fistula formation is not known. It has been thought to be due to the extension of infection/inflammation of superficial tissues (hydradenitis) or anal sacs. Conformation has also been thought to play a role in the formation of fistulas, including a sunken or recessed anus, and a tight tail base. These anatomic peculiarities may result in a persistent fecal film in the perineal region predisposing to infection.

Probably the most significant change in the treatment of canine perianal disease occurred with the report that the immunosuppressive drug cyclosporine results in significant improvement or resolution of perianal fistulas. After 16 weeks of treatment, fistulas had healed in 17/20 (85%) dogs. It is unclear if perianal fistulas are a primary immune-mediated disease or if there is simply an immune-mediated component to the disease. Humans with a form of chronic inflammatory bowel disease (Crohn's disease) may also develop perianal fistulation which often responds to cyclosporine. In another canine study 9/27 (33%) of German Shepherds with fistulas and histologically confirmed colitis had resolution of their fistulas after being placed on high doses of corticosteroids and a hypoallergenic diet. I typically start my canine patients with perianal fistulas on 3 mg/kg of microemulsified cyclosporine (Neoral®- Novartis), PO, BID. Neoral comes in 50-ml vials (approximately $300/vial) and the proper dose can be pulled up in a syringe and then added to an empty gelatin capsule. It is also available in 100-mg gelcaps, which is often close to the proper dose for the typical German Shepherd with this disease. The veterinary approved version Atopica (also from Novartis) comes in 10, 25, 50 and 100 mg capsules, and is also less expensive. I typically check the patient's trough plasma concentration of cyclosporine 2 weeks after beginning the medication and make appropriate adjustments in dosing based on the results. The target concentration is between 300-500 ng/ml using an HPLC assay. With the TdX assay used at NCSU our target is between 500-750 ng/ml. Make sure you check which assay your laboratory is using. Most labs associated with human hospitals run this assay, but may not for veterinary patients, or may be quite expensive. Dosage is increased if the trough concentration is low, particularly if there has been minimal or no response after one month on the drug. Trough concentrations as low as 75 ng/ml (HPLC) may be effective in some dogs. Decrease in fistula size is not usually seen for the first 2 weeks. However, many clients report an improvement in their dog's energy level, decreased licking at the area and diminished tenesmus within the first 2 weeks. The cyclosporine should be kept in a dark cupboard at room temperature. Blood samples should be drawn in the morning, 12 hours after the last evening dose, and prior to giving the dog its morning medications. Have the owner mail an EDTA (purple-topped) blood tube to the laboratory by courier (eg. Fed Ex).

Unanswered questions regarding cyclosporine and perianal fistulas include:

1. What is the proper duration of treatment? I will keep my patients on the drug for at least 2 weeks after complete resolution of fistulas based on visual examination. It is unclear if these dogs should be treated longer in order to keep the disease in remission, or if it is better to treat only during recurrent episodes. Small fistulas recurred in 7/17 dogs 2-24 weeks after discontinuing therapy.

2. What is the underlying etiology/reason that cyclosporine works? What is occurring at a cellular level before, during and after treatment with cyclosporine? All 27 dogs with perianal fistulas in one study, and 9/18 dogs in another study had histologic evidence of colitis. The link between colitis and perianal fistula formation is unclear. Serial histologic sampling from dogs treated with cyclosporine has not been reported. Follow-up biopsies taken from dogs treated with corticosteroids and dietary therapy failed to show any change in severity of colitis in both dogs that responded, and those that failed, to respond to medical management.

3. Why do some dogs respond and others do not? One study showed no difference between human responders and non-responders with Crohn's disease in the mean blood or intestinal tissue concentrations of cyclosporine. The use of new treatments such as a hypoallergenic diet given previous findings of colitis and response to dietary/steroid therapy in some cases; however, prospective clinical trials focusing on different diets are lacking.

Tacrolimus ointment applied to the affected area has also been shown to have some effect. It is available as a 0.1% ointment (Protopic: Astellas Pharma – formerly Fujisawa). When used as the sole therapy for 16 weeks, 5/10 dogs showed a complete response. I have used tacrolimus ointment in perianal fistula patients that are showing either a limited response to cyclosporine, or have recurrence of fistulas following discontinuation of cyclosporine therapy. In such cases, I try to get the medical management of these fistulas is lacking.

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fistulas back into remission with cyclosporine, start application of tacrolimus ointment, and then discontinue cyclosporine while continuing tacrolimus application. Although this appears to have been an effective treatment strategy in several cases, results are purely anecdotal and a blinded prospective study needs to be performed. It should be noted that the FDA recently placed a warning on the use of this drug in people because animal studies have shown prolonged use may predispose to the development of some forms of cancer. It is not yet approved for veterinary use. Our pharmacist recommends the following precautions: owners should wear gloves when applying; do not use it indefinitely; use the minimal amount to control symptoms; consult a veterinarian if skin masses or lymph node enlargement is noted; and keep the drug away from children or adults with weakened immune systems.

Given that many affected dogs also have colitis, pretreatment colonic biopsy followed by treatment with sulfasalazine and/or piroxicam (assuming no corticosteroid use) appears to be a rational although unproven approach.

5. Should other medications be given to inhibit cyclosporine metabolism and thereby decrease the cost of treatment (eg. ketoconazole)? Several studies have shown that the dose of cyclosporine can be reduced if ketoconazole is given at the same time.\textsuperscript{8,9} Ketoconazole acts as a competitive inhibitor of cyclosporine metabolism. The typical dose for dogs is 5mg/kg, PO, BID. The main advantage of using ketoconazole is the decreased cost associated with administering less cyclosporine. I have used erythromycin (5mg/kg, PO, BID) in some cases to achieve the same effect. Whenever a drug is used for this purpose, cyclosporine levels and chemistry panels should be performed every few weeks at first, so that adjustments in dosing can be made. Liver enzymes should be monitored and ketoconazole discontinued if they rise. Renal damage may result if cyclosporine concentrations are extremely elevated.

I currently recommend cyclosporine therapy for the treatment of perianal fistulas; however, medication costs, the surgical options and their potential complications need to be discussed, so that the owner can come to an informed decision. In addition, excision of persistent or recurrent fistulas may be required.

References