Cyclosporine and ketoconazole for the treatment of perianal fistulas in dogs

Alison J. Patricelli, DVM; Robert J. Hardie, DVM, DACVS; Jonathan F. McAnulty, DVM, PhD

Objective—To evaluate efficacy and cost of using cyclosporine and ketoconazole for the treatment of perianal fistulas in dogs.

Design—Clinical trial.

Animals—12 dogs with perianal fistulas.

Procedure—Dogs received cyclosporine and ketoconazole orally (target whole blood trough cyclosporine concentrations of 400 to 600 ng/ml). Study endpoints were resolution of clinical signs, remission, and recurrence of disease. Adverse effects and cost of medications were reported. Results were compared with those from previous studies in humans and in dogs in which single agent cyclosporine treatment for perianal fistulas was used.

Results—All dogs had resolution of clinical signs. Eight dogs went into remission; however, 5 of those 8 had recurrence of fistulas. Adverse effects of treatment were minimal and well tolerated. Cost of treatment was comparable to traditional surgical options and less than single agent cyclosporine treatment.

Conclusions and Clinical Relevance—Administration of cyclosporine with ketoconazole is an effective and cost-comparable treatment for perianal fistulas in dogs. (J Am Vet Med Assoc 2002;220:1009–1016)

Perianal fistulas are chronic, painful, progressive inflammatory lesions of the perianal, anal, and perirectal tissues. Perianal fistulas have been reported in humans in association with chronic granulomatous inflammatory disease (Crohn's disease) and in dogs. In dogs with perianal fistulas, German Shepherd Dogs are overrepresented, with 1 study reporting German Shepherd Dogs as 84% of overall cases.

Clinical signs of perianal fistulas include tenesmus, self-mutilation, dyschezia, constipation, weight loss, lethargy, increased frequency of defecation, pain on examination of the tail and perianal region, and perianal licking. Lesions may vary in appearance from superficial pinpoint fistulas to large ulcerated areas, sometimes extending deep into the perianal region. Lesions may also involve the anal sacs and rectal tissue. On rectal examination, thickening and fibrosis of the anus and rectum can be palpated.

Medical and surgical treatments of perianal fistulas have been recommended. Until recently, medical treatment included antibiotics, cleansing, anti-inflammatory drugs, and analgesics. Multiple reports have shown these treatments to be palliative at best. Traditionally, the treatment of choice for dogs with moderate or severe disease was surgery, with success of medical treatment feasible primarily in dogs with more mild disease.

In seeking a more effective treatment for perianal fistulas, efforts have been made to identify the etiopathogenesis of the disease. Anatomic factors and immune-mediated mechanisms have been suggested. Recent recommendations for the treatment of perianal fistulas in dogs have been aimed at the immune cascade involved in the disease process. Both high doses of prednisone and cyclosporine have been used with remission rates of 33% and 72 to 100%, respectively. Recurrence rates of perianal fistulas after cessation of prednisone have not been reported. Both high dose (400 to 600 ng/ml whole blood trough concentrations) and lower dose (100 to 300 ng/ml whole blood trough concentrations) cyclosporine treatment regimens have been reported to be successful in inducing remission of perianal fistulas in dogs.

In 4 reports in dogs, recurrence rates of perianal fistulas following cyclosporine treatment were 17, 30, 36, and 40%. Follow-up times in these reports ranged from 4 to 20 months.

Cyclosporine is expensive and is rapidly metabolized in the dog. Clearance rates of cyclosporine have been shown to be 2.8 times faster in dogs than in humans. Dosing of cyclosporine to achieve specific whole blood trough concentrations in dogs can also result in wide variations in the achieved concentration over a single dosing cycle. A drug regimen that aimed at reducing the amount of cyclosporine necessary to achieve desired whole blood trough concentrations and to homogenize the concentrations of this drug in the blood over the dosing cycle would be advantageous. Such a regimen would have considerable economic benefits and may have positive impacts on the efficacy and incidence of adverse effects associated with cyclosporine for the treatment of perianal fistulas in dogs.

Ketoconazole is an adjuvant agent that can be used to slow the clearance of cyclosporine and reduce the amount of cyclosporine needed to achieve target whole...
blood concentrations. Ketoconazole has been shown to decrease the systemic clearance of cyclosporine in dogs through inhibition of hepatic P450III A microsomal enzymes. In dogs, ketoconazole administration has been shown to be effective in obtaining higher blood concentrations of cyclosporine.

One experimental study reported a 75% dose reduction in cyclosporine when combined with ketoconazole (13 mg/kg [5.9 mg/lb], PO, once daily). In 1 report of 4 dogs with perianal fistulas, a 75% dose reduction in cyclosporine was achieved, using ketoconazole at 2.2 to 8.5 mg/kg (1.0 to 3.86 mg/lb, PO, once daily). Adverse effects were mild weight loss and hypertrichiasis in 2 dogs in this group. Remission rates were 100% in this limited study; however, follow-up times were not available so recurrence rates are unknown.

The purpose of the study reported here was to evaluate the use of high doses of cyclosporine and ketoconazole for the treatment of perianal fistulas in dogs. Our hypothesis was that high doses of cyclosporine and ketoconazole would be effective in inducing resolution of clinical signs and remission of disease in dogs with perianal fistulas and that the adverse effects of this regimen would be minimal. We also hypothesized that cyclosporine and ketoconazole treatment would represent a regimen that is cost comparable to traditional surgical options and is less expensive than single agent cyclosporine treatment.

Materials and Methods

Dogs—Twelve dogs with perianal fistulas were evaluated. The owner of each dog was interviewed to determine the duration of disease, clinical signs, and nature of any previous treatment. In all dogs, a complete physical examination was performed prior to treatment. If dogs were resistant to examination of the perianal and rectal areas, they were sedated to complete the examination. Fistula size and depth were measured, using a blunt probe.

Fistula grading—Perianal fistulas were identified and graded according to the following grading scale: mild = superficial (< 3 mm × 3 mm × 5 mm) tract or tracts with mild inflammation encompassing 0 to 90° of rectal circumference; moderate = superficial or deep tracts with moderate inflammation encompassing up to 270° of rectal circumference; and severe = multiple deep tracts or superficial lesions encompassing 270 to 360° of rectal circumference.

Dosing—All dogs were given cyclosporine and ketoconazole. Cyclosporine was administered orally twice daily in 8 dogs at an initial dose of approximately 2.5 mg/kg (1.1 mg/lb) and orally once daily in 4 dogs at an initial dose of approximately 4 mg/kg (1.8 mg/lb). All dogs received ketoconazole once daily at an initial dose of approximately 8 mg/kg (3.6 mg/lb), administered orally concurrently with cyclosporine. Trough cyclosporine concentrations were assayed by use of high performance liquid chromatography (HPLC), using whole blood drawn just before administration of drugs, on day 5 of treatment and monthly thereafter. Cyclosporine doses were adjusted to attain whole blood trough target concentrations of 400 to 600 ng/ml.

The first study endpoint was resolution of disease (complete healing of all lesions). Dogs were rechecked monthly until these endpoints were achieved. Any adverse effects of medications were recorded as reported by owners at recheck examinations or via additional phone conversations. Complete blood count and serum biochemical analyses were performed at initial and recheck examinations at the individual clinician’s discretion.

All dogs that underwent remission were followed to a third study endpoint of recurrence of disease. If perianal fistulas recurred, then owners were given a choice of a second course of high-dose cyclosporine and ketoconazole, low-dose cyclosporine and ketoconazole, or combination high-dose followed by low-dose treatment. All dogs were then followed until resolution of clinical signs and second remission.

Cost analysis—Cost of treatment was determined, using the lowest medication dose and the highest medication dose from the dose range of all dogs, with a mean treatment time of 16 weeks. Doses were rounded to the nearest capsule size. Treatment costs were calculated, using medication prices of cyclosporine, 100 mg ($6.07/capsule); cyclosporine, 25 mg ($1.52/capsule); and ketoconazole, 200 mg ($0.85/tablet). Costs were then compared with previous reports of single agent cyclosporine therapy for treatment of perianal fistulas in dogs.

Statistical analyses—Data were compared by use of the t-test. Duration of disease prior to treatment and remission, duration of disease prior to treatment and recurrence, duration of treatment time and remission, and duration of treatment time and recurrence were analyzed. Values of P < 0.05 were determined significant.

Results

Dogs—Breeds represented in this study included German Shepherd Dogs (n = 9), Border Collie (1), English Bulldog (1), and German Shepherd cross (1). Ages ranged from 4 to 9 years with a mean of 4.7 years. Three dogs were sexually intact males, 3 were castrated males, 1 was a sexually intact female, and 5 were spayed females. Body weights ranged from 23 kg (50 lb) to 41.6 kg (91.5 lb).

Prior treatment and clinical signs—All dogs had received prior treatment for perianal fistulas, including antibiotics, corticosteroids, surgery, dietary changes, and enemas. Three dogs had been previously treated with low doses of cyclosporine, with trough whole blood concentrations maintained between 100 and 300 ng/ml. Clinical signs at examination included tenesmus, dyschezia, perianal licking, constipation, pain on raising the tail, weight loss, lethargy, and diarrhea. Mean duration of clinical signs prior to examination was 92.4 weeks (range, 4 to 260 weeks).

Physical examination findings and fistula grading—On physical examination, 1 dog was severely cachectic. I had a rectal stricture from previous surgery, and 1 had an abscessed and dehisced surgical site from previous anal saccectomy. Fistulas were graded as mild in 1 dog (Fig 1), moderate in 4 dogs (Fig 2) and severe in 7 dogs (Fig 3). All dogs were painful on examination of lesions, and 10 required heavy sedation for fistula examination and measurement. After 3 to 4 weeks of high-dose cyclosporine and ketoconazole treatment, 11 dogs allowed complete external examination of fistulous tracts without sedation.

Cyclosporine and ketoconazole dosing and adverse effects—Initial cyclosporine doses ranged from 1.9 to 3.5 mg/kg (0.86 to 1.6 mg/lb, PO, q 12 h [n
and from 2.5 to 5.5 mg/kg (1.1 to 2.5 mg/lb, PO, once daily [n = 4]). The initial dose of ketoconazole ranged from 5.1 to 11 mg/kg (2.3 to 5.0 mg/lb, PO, once daily [n = 12]). Mean initial whole blood trough concentration was 607 ng/ml (range 130 to 1398 ng/ml). Mean duration of high-dose cyclosporine and ketoconazole treatment was 16.2 weeks (range, 6.5 to 52 weeks).

Adverse effects of medication included vomiting (n = 3), hypertrichiasis (3), weight loss (2), hyporexia (6), and icterus (1). One dog had a shifting leg lameness during the course of treatment; however, panosteitis was confirmed radiographically.

In 2 dogs, owners chose to stop medications because of perceived adverse effects. One dog was withdrawn from the study during week 4 because of hyporexia. The owners perceived that the hyporexia was from cyclosporine; however, this dog had a low cyclosporine trough concentration (135 ng/ml) at the time of signs. When the dog was entered into the study, it had also been changed from a mostly raw meat diet to a limited antigen diet of fish and potato. Because the owners stopped medications and returned the dog to a more palatable diet at the same time, we were unable to assess whether the hyporexia resulted from the medications. This dog was excluded from all further analysis because of the short duration of treatment.

In another dog, the owners chose to withdraw medications because of hyporexia and icterus after 8 weeks of high-dose cyclosporine treatment. At the time of medication withdrawal, this dog had a whole blood trough concentration of 800 ng/ml. For all other dogs, adverse effects were reported as mild and tolerable by owners.

Resolution of clinical signs—Clinical signs resolved in all dogs within 9 weeks of start of treatment (mean, 4.3 weeks; range, 1 to 9 weeks).

Remission of disease—Significant improvement of perianal fistulas was seen in all dogs, with clinical remission in 8 dogs (Fig 4 and 5). Mean time to remission was 13.9 weeks (range, 4 to 49 weeks). The 1 dog with mild disease underwent remission 4 weeks from the start of treatment. Two of 3 dogs with moderate disease underwent remission, with a mean time to remis-

Figure 1—Mild perianal fistulas in a dog.

Figure 2—Moderate perianal fistulas in a dog.

Figure 3—Severe perianal fistulas in a dog.

Figure 4—Appearance of perianal fistulas in a dog after 6 weeks of receiving high doses of cyclosporine and ketoconazole. Notice the minimal inflammation. This dog had severe fistulas at the time of initial examination.
Perianal fistulas improved dramatically with high-dose cyclosporine and ketoconazole treatment in the 3 dogs that did not undergo complete remission. In 2 of these 3 dogs, fistulas were reduced to pinpoint lesions (<2 mm × 2 mm). Both dogs were changed to low-dose cyclosporine treatment after an initial 16 weeks of high-dose treatment. Both dogs have remained free of clinical signs and have had no progression of disease after 8 weeks of low-dose treatment. In the remaining dog that did not undergo remission, multiple superficial lesions were present 8 weeks after initiation of high-dose treatment. At that time, the dog had signs of icterus and hyporexia, and the owners chose to withdraw medications and pursue surgical treatment.

The mean duration of disease prior to examination was not significantly different for dogs that underwent remission (mean, 109 weeks; range, 4 to 260; n = 8) and those that did not (mean, 24 weeks; range, 16 to 32; n = 2; P = 0.07). The mean duration of high-dose cyclosporine and ketoconazole treatment was not significantly different for dogs that underwent remission (mean, 17.3 weeks; range, 6.5 to 53 weeks; n = 8) and dogs that did not undergo remission (mean, 13.7 weeks; range, 8 to 16 weeks; n = 3; P = 0.52).

**Recurrence of disease**—Recurrence of perianal fistulas occurred in 5 of 8 dogs that underwent clinical remission. Mean time to recurrence was 12.4 weeks (range, 5.5 to 22 weeks). All dogs with recurrence of fistulas had moderate (n = 2) or severe disease (3) at initial examination.

Dogs that had recurrence of perianal fistulas had significantly longer duration of disease prior to examination than dogs that did not have recurrence. Mean duration of fistulas for dogs that had recurrence was 166.4 weeks (range, 52 to 260 weeks; n = 5). Mean duration of fistulas for dogs that did not have recurrence was 15 weeks (range, 4 to 24 weeks; n = 3; P = 0.03).

One dog had recurrence 14.5 weeks after the dosage of cyclosporine was reduced, and whole blood trough concentrations decreased to < 100 ng/ml. Four dogs had recurrence after cessation of medication, with a mean time to recurrence of 11.8 weeks (range, 5.5 to 22 weeks).

The mean high-dose cyclosporine and ketoconazole treatment time of dogs that had recurrence of perianal fistulas was approximately half that of the mean total treatment time of dogs that did not have a recurrence. Mean treatment times were 12.9 weeks (range, 6.5 to 19 weeks; n = 5) and 24.7 weeks (range, 10 to 53 weeks; n = 3) in these groups, respectively. Because of the variation among dogs, these values were not significantly different (P = 0.49).

**Outcomes**—After recurrence of perianal fistulas, high-dose cyclosporine and ketoconazole treatment was restarted in 4 dogs. At the time of final follow-up, these 4 dogs were still undergoing treatment, with a mean treatment time of 9 weeks (range 6.5 to 11 weeks). All 4 dogs had a second resolution of clinical signs. Mean time to resolution of clinical signs was 4.6 weeks (range, 3 to 6 weeks). One dog underwent a second complete remission 5.5 weeks after restart of high-dose treatment.

One dog that had recurrence of perianal fistulas is presently on a long-term maintenance treatment regimen (118 weeks). Treatment in this dog was reduced to low-dose cyclosporine (1.6 mg/kg [0.73 mg/lb], PO, q 12 h) and ketoconazole (7.3 mg/kg [3.3 mg/lb], PO, once daily) at the owner's request after 6 weeks of the second course of high-dose treatment. This dog remains free of clinical signs on low-dose treatment but has not undergone remission.

One dog had recurrence of perianal fistulas after a dose reduction resulted in whole blood trough cyclosporine concentrations of < 100 ng/ml. The dog was then placed on a low-dose regimen of cyclosporine and ketoconazole. This dog underwent complete remission 3 weeks after whole blood trough cyclosporine concentration of 143 to 163 ng/ml was reached. The owner has chosen to leave this dog on low-dose treatment indefinitely.

**Surgery**—Five dogs in the study underwent surgery during their course of treatment. Surgical treatment of perianal fistulas did not facilitate remission in any case. One dog required initial debridement of an abscessed and dehisced surgical site. No effort was made to resect the multiple perirectal and rectal fistulas at surgery. One dog underwent anal sacculectomy and fistula excision after 8 weeks of high-dose cyclosporine and ketoconazole treatment. Fistulas had improved from severe to multiple superficial lesions at the time of surgery. The owners did not restart medications after surgery, and multiple fistulas were evident within 5 weeks. Fistulas were excised in another dog after 8 weeks of high-dose cyclosporine and ketoconazole treatment. Medications were discontinued after

---

**Figure 5**—Dog in Figure 1 after 4 weeks of cyclosporine treatment. This dog underwent remission of disease, with complete healing of all fistulas.
surgery, and multiple fistulas were evident within 6 weeks. At that time the dog was restarted on high-dose treatment.

Cryosurgery was performed on multiple superficial lesions 19 and 27 weeks after initiation of high dose treatment in 1 dog. Cyclosporine and ketoconazole treatment was continued after surgery. Remission did not occur until 24 weeks after the second surgical procedure. Another dog underwent cryosurgery 6 weeks after a second course of high-dose cyclosporine and ketoconazole treatment for recurrence of perianal fistulas. After surgery, the owners chose to put the dog on low-dose treatment. This dog remains free of clinical signs, but fistulas persist after 118 weeks of low-dose treatment.

Cost analysis—The mean cost of high-dose cyclosporine and ketoconazole treatment was $653.60 for the lowest prescribed dose (cyclosporine, 2.5 mg/kg, PO, once daily; ketoconazole, 5.1 mg/kg, PO, once daily), and $1,395.80 for the highest prescribed dose (cyclosporine, 3.5 mg/kg, PO, q 12 h; ketoconazole, 11 mg/kg, PO, once daily; 16-week treatment cycle). This cost represents a range of $20.25/kg ($44.50/lb) to $49.45/kg ($108.79/lb). For the 4 dogs on low-dose treatment, treatment costs were $71.10/mo in 2 dogs, and $129.45/mo in the remaining 2 dogs. This treatment resulted in costs of $2.49/kg ($5.48/lb) and $3.54/kg ($7.80/lb).

Previous studies in which single agent cyclosporine treatment was used for treatment of perianal fistulas in dogs reported dose ranges of 2.7 mg/kg (1.2 mg/lb, PO, q 12 h) to 10 mg/kg (4.5 mg/lb, PO, q 12 h).2,21,22 Using these costs and the body weights of the dogs in our study, the cost of single agent cyclosporine treatment would range from $1,019.76 for the lowest prescribed dose to $5,438.72 for the highest prescribed dose (16-week treatment cycle). These costs equate to $31.60/kg ($69.52/lb) to $168.54/kg ($370.78/lb).

The cost of high-dose cyclosporine and ketoconazole treatment presented here thus represents a 36 to 71% savings over previous reports of single agent cyclosporine treatment.

Discussion
Recent reports have helped to contribute to a clearer understanding of the underlying etiopathogenesis of perianal fistulas in dogs. Anatomic factors such as an increased density of apocrine sweat glands in the cutaneous zone of the anal canal of German Shepherd Dogs have been implicated in the development of the fistulous tracts.17 This finding may be 1 reason why German Shepherd Dogs are overrepresented in this and other studies of dogs with perianal fistulas.

German Shepherd Dogs are also predisposed to multiple immune-mediated diseases. Recent work in German Shepherd Dogs with inflammatory bowel disease and small intestinal bacterial overgrowth revealed increased concentrations of interleukin (IL)-2, IL-5, IL-12p40, tumor necrosis factor (TNF)-α, and TGF-β in intestinal tissues.27 Histologic examination of fistulous tracts and associated tissues in dogs with perianal fistulas has revealed inflammation with hidradenitis, epithelial necrosis at the follicular infundibulum, aggregates of eosinophils, and an intense inflammatory response with plasma cells, lymphocytes, macrophages, and perivascular lymphoid nodules. Further research has indicated that CD3+ T lymphocytes and IgA- and IgG-secreting B lymphocytes to be prominent in the inflammation of perianal fistulas.

Inflammatory bowel disease, small intestinal bacterial overgrowth, and perianal fistulas are examples of diseases that result from a dysregulated immune response.27,28 Specifically, there is a loss of balance between pro-inflammatory and anti-inflammatory stimuli. As such, new approaches to the treatment of these diseases have been aimed at addressing the underlying immune system and its regulation.

Humans with chronic granulomatous inflammatory disease and perianal fistulas also have immune-dysregulation with disruption of normal T-cell regulatory mechanisms. Specifically, T-helper cell 1 pathways are up-regulated in patients with this disease, with increased concentrations of IL-1, TNF-α, IL-6, and interferon (IFN). These patients have also have deficiencies of IL-10, a potent anti-inflammatory cytokine.29

Glucocorticoids shift T and B cells to the bone marrow, decrease monocyte chemotaxis and function, decrease IL-1 production, and reduce prostaglandin and leukotriene production.29 In 1 study, glucocorticoids induced remission in 48% of patients with chronic granulomatous inflammatory disease; however, 20% of patients became steroid-resistant within 30 days of treatment, and 56% of patients became resistant within 1 year. Additionally, 36% of patients had recurrence within 1 month of dose reduction or stoppage.

In dogs, treatment with high doses of prednisone (2 mg/kg [0.9 mg/lb], PO, q 24 h, tapered) and dietary therapy resulted in improvement of perianal fistulas in 18 of 27 (66%) of dogs in 1 study, with complete resolution of the disease in 9 (33%) dogs.26 Of the 27 dogs treated, 6 (22%) remained clinically affected by the disease, with signs of hematochezia, tenesmus, and increased frequency of defecation. It is also important to state that only 1 of 13 (8%) dogs with severe disease had remission. No dogs were followed beyond disease remission; thus, the incidence of recurrence remains unknown. Signs of iatrogenic hyperadrenocorticism, nonseptic suppurative inflammation of the stifle, deep pyoderma, and pyogranulomatous cellulitis were reported during treatment with high doses of prednisone. The overall complication rate for this treatment was 15% (4/27). Persistence of clinical signs, adverse effects from glucocorticoids, and modest remission rates have led to further research into more effective treatments for perianal fistulas in humans and dogs.

Cyclosporine is a potent immunosuppressive drug that blocks production of and responsiveness to IL-2, IL-6, and γ-IFN by CD4+ T lymphocytes.31-33 Specifically, cyclosporine is thought to inhibit calcineurin-mediated regulation of cytokine transcription and the generation of cytotoxic T cells. Cyclosporine also indirectly inhibits growth and differentiation of B

JAVMA, Vol 220, No. 7, April 1, 2002 1013

Scientific Reports: Original Study
Cyclosporine has also been reported as a treatment of perianal fistulas in humans with chronic granulomatous inflammatory disease. High doses administered IV, low doses administered orally, and combinations of these have been used. In 1 study of 16 patients in which other treatments failed, high doses of cyclosporine administered IV resulted in improvement of fistulas in 88% of patients, with 44% attaining remission of disease. In another study of 5 patients, 100% improved with high doses of cyclosporine administered IV, with 83% of fistulas closing. These patients were then changed to low doses administered orally (whole blood trough concentrations of 100 to 200 ng/ml), with 33% of patients experiencing recurrence of disease.

Low-dose cyclosporine therapy has been tested extensively in humans with chronic granulomatous inflammatory disease. In a study of 305 patients treated for 18 months, the cyclosporine group scored less favorably in measured variables of disease status than the placebo group. In a study of 140 patients, there were no significant measured differences in any disease variables between the cyclosporine and the placebo groups.

Cyclosporine is currently used as a steroid-sparing agent in patients with chronic granulomatous inflammatory disease. However, in 1 study, cyclosporine had to be withdrawn in 43% of patients because of adverse effects, and 86% of patients experienced recurrence after doses were weaned below blood concentrations of 74 ng/ml.

Our study included 3 dogs that had received low-dose cyclosporine treatment prior to beginning high-dose treatment. In previous reports of dogs, low doses of cyclosporine have been speculated to be adequate to induce remission of perianal fistulas. For 2 of 3 dogs in our study, low doses of cyclosporine had not been successful in inducing remission of perianal fistulas.

Of the 2 dogs in which low-dose treatment did not work, 1 dog had multiple superficial lesions after 7 months of low-dose treatment (trough concentration of 195 ng/ml), and the other dog had minimal improvement in clinical signs and continued severe disease after 4 weeks of treatment (trough concentration of 135 ng/ml). Both dogs had complete resolution of clinical signs and considerable improvement of perianal fistulas after 4 weeks of high-dose treatment. It is possible that these dogs represent a subset of the disease population that is more resistant to cyclosporine and has a higher degree of immune dysregulation, thereby requiring higher blood concentrations of cyclosporine to achieve a clinical response. This scenario would parallel descriptions of the response of chronic granulomatous inflammatory disease to cyclosporine in the human literature; however, further investigation with larger numbers of dogs is needed.

The remaining dog underwent a prior complete remission after 6 weeks of low-dose treatment (total treatment cycle of 12 weeks), but fistulas recurred 32 weeks after cessation of medication. This dog underwent a second complete remission after 18 weeks of high-dose treatment. After this second remission, the cyclosporine was reduced to low dose. This dog remained in remission until trough cyclosporine blood concentrations fell below 100 ng/ml. At that time, the dog underwent a second recurrence of perianal fistulas. After cyclosporine dose adjustment to achieve trough blood concentrations of 100 to 300 ng/ml, the dog underwent a third clinical remission that has been maintained for 8 weeks. This dog, unlike the 2 other dogs, did undergo remission with low-dose cyclosporine and ketoconazole treatment.

There are few previous reports of cyclosporine use in dogs with perianal fistulas. One study of 20 dogs reported improvement of fistulas in all cases, with complete healing of lesions in 85% of the dogs. Recurrence rates were 40%, with follow-up times of 10 to 15 months after cessation of treatment. Treatment courses varied, with most dogs receiving 16 weeks of cyclosporine with target whole blood trough concentrations of 400 to 600 ng/ml. Another study of 6 dogs reported improvement in all dogs and complete resolution in 5 dogs. Follow-up time was 4 to 14 months, with a mean of 7.7 months. One dog developed recurrence 8 weeks after treatment. In that study, treatment courses varied from 10 to 20 weeks, with target whole blood trough concentrations of 400 to 600 ng/ml. One study of 26 dogs revealed clinical improvement in 25 (96%) dogs and complete resolution in 18 (72%) dogs. Mean duration of follow-up was 6.8 months, with 9 (36%) dogs developing recurrence. In these dogs, whole blood trough concentrations were not measured.

To our knowledge, combination cyclosporine and ketoconazole treatment has only been reported in abstract form in 4 dogs with perianal fistulas. However, the unique aspects of metabolism of cyclosporine and its expense make combining the drug with an inhibitor of its metabolism advantageous. Previous experimental studies in dogs have revealed that concurrent administration of ketoconazole and cyclosporine increased the half-life of cyclosporine over 2-fold, increased stable blood concentrations of cyclosporine, and reduced the concentration of a number of cyclosporine metabolites. These effects were observed at ketoconazole doses of 2.5 mg/kg (PO, once daily) and were maximal at 10 mg/kg (PO, once daily), with an 85% reduction in total body cyclosporine clearance.

Ketoconazole has also been shown to have in vivo activity against various bacterial, fungal, and yeast species. In human transplant patients, low-dose treatment with ketoconazole (10 mg/kg) has been associated with reductions in post-operative bacterial, viral, and fungal infections when combined with other immune-modulating agents. It is possible that the low-dose ketoconazole administered to the dogs of this study had similar beneficial effects; however, this effect should be further investigated.

Adverse effects of ketoconazole administration in dogs and humans include various hepatic reactions.
These reactions can result in transient increases in hepatic enzyme activities, reversible cholestatics, and possible acute hepatic necrosis. Previous experimental studies in dogs, however, have shown that concurrent administration of ketoconazole and cyclosporine resulted in no change in the biochemical indices of liver function.

Our results are consistent with data allowing cyclosporine dose reductions of 50 to 75% to achieve target whole blood concentrations with concurrent ketoconazole administration. The cost of high-dose cyclosporine and ketoconazole treatment regimens is comparable to traditional surgical options, with costs ranging from $560 to $1,600 (mean body weight, 32 kg) for a 16-week treatment cycle. The cost range represents a 36 to 71% savings over single agent cyclosporine treatment. Low-dose treatment introduced early or late in the course of disease will also affect costs; some dogs in our study have continuing monthly maintenance costs of $71 to $130.

The incidence of recurrence in our study is similar to that reported in humans receiving cyclosporine for the treatment of perianal fistulas. However, recurrence rates reported here were higher than in previous reports in dogs. It is possible that the long duration of fistulas prior to presentation (mean, 92.4 weeks) in these dogs contributed to this result. In our study, dogs that experienced recurrence of disease had significantly longer duration of fistulas prior to presentation than those that did not experience recurrence. This finding is similar to a previous report of perianal fistulas in 20 dogs. Dogs with a long previous duration of fistulas may have an immune system that is more dysregulated and more prone to recurrence once immunosuppressive medications have been discontinued. Because of the high recurrence rate in dogs with long duration of fistulas prior to treatment, we recommend initiation of high dose cyclosporine and ketoconazole early in the disease course.

Low-dose cyclosporine and ketoconazole therapy induced remission in 1 dog in our study; however, low-dose therapy was more commonly used to maintain resolution of clinical signs or remission in dogs with resistant disease. Though results of low-dose cyclosporine therapy in humans have been disappointing, more work with larger numbers of dogs is needed to establish the effect of low-dose therapy in dogs with perianal fistulas.

References


