

Cyclosporine in Veterinary Dermatology

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KEYWORDS

- Cyclosporine • Atopic dermatitis • Immune-mediated skin disease • Perianal fistula
- Sebaceous adenitis

KEY POINTS

- Cyclosporine is an immunomodulatory medication that is approved for atopic dermatitis in dogs and allergic dermatitis in cats.
- Cyclosporine has been used to manage a variety of immune-mediated skin diseases including perianal fistulas and sebaceous adenitis.
- Drug interactions with cyclosporine are commonly reported caused by the shared metabolic pathways involving cytochrome P450 and/or competition with P-glycoprotein.
- The most commonly reported side effects caused by cyclosporine are gastrointestinal in nature; other reported side effects are typically reversible with discontinuation of cyclosporine.

INTRODUCTION

Cyclosporine A (CsA) is an immunomodulatory medication that was initially isolated from the fungus *Tolypocladium inflatum*.¹ It has been successfully used in the treatment of a variety of inflammatory and immune-mediated skin diseases. This article reviews the use of CsA in veterinary dermatology, including its mechanism of action, pharmacokinetics, drug interactions, side effects, and relevant clinical updates. Dermatologic indications including atopic/allergic dermatitis, perianal fistulas, sebaceous adenitis, and other immune-mediated skin diseases are discussed.

FORMULATIONS OF CYCLOSPORINE

In humans, CsA was first developed as a vegetable oil formulation (Sandimmune; Novartis Pharmaceuticals) that is highly dependent on biliary excretion for absorption.² A newer microemulsified (ME; ie modified) CsA product (Neoral; Novartis Pharmaceuticals) was developed that improves oral bioavailability, decreases individual variability

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in absorption, and decreases the effect of bile secretion on absorption; approved generic preparations of modified CsA are available for use in humans.² In humans, the bioavailability of the ME form of CsA is 30% to 40%, compared with 20% to 30% for the nonmodified formulation.³ In canine patients, the ME form offers an approximate 35% bioavailability, compared with 20% to 25% with the vegetable oil formulation.^{2,4} In veterinary medicine, modified CsA (Atopica, Novartis Animal Health) is approved for use in dogs for atopic dermatitis; this product is available in 10, 25, 50, and 100 mg soft gelatin capsules.⁵ ME CsA (Atopica for Cats, Novartis Animal Health) was recently approved for the treatment of allergic dermatitis in cats; this product is available as an oral solution with a concentration of 100 mg/mL.⁶

MECHANISM OF ACTION

CsA, a calcineurin inhibitor, is an immunosuppressive medication that inhibits T-cell activation.¹ CsA binds to the intracellular protein cyclophilin-1; the cyclophilin-CsA complex inhibits calcineurin, preventing the dephosphorylation/activation of nuclear factor of activated T cells (NFAT).² NFAT helps regulate the production of several important proinflammatory cytokines including interleukin (IL)-2, IL-4, interferon (IFN)- γ , and tumor necrosis factor (TNF)- α .⁷ Inhibition of IL-2, a potent T-cell growth promoter and activator, is most commonly implicated as the main mechanism of immunosuppression.^{7,8} In feline lymphocytes in vitro, CsA has been shown to decrease IL-2, IL-10, IFN- γ , and granulocyte-macrophage colony-stimulating factor production.⁹ A recent article used flow cytometry to assess the pharmacodynamic effect of CsA on the production of various cytokines in dogs.¹⁰ High-dosage CsA (10 mg/kg twice daily) resulted in significant decreases in IL-2 and IFN- γ expression, but not IL-4 expression.¹⁰ Low-dosage CsA was associated with a significant decrease in IFN- γ expression, whereas IL-2 expression was not affected.¹⁰ CsA affects several cells in the skin, including T cells, dendritic cells, Langerhans cells, keratinocytes, mast cells, and eosinophils.^{2,11} It impairs the ability of dendritic cells to stimulate proliferation of T cells, decreases the number and activity of Langerhans cells in the epidermis, decreases cytokine secretion by keratinocytes, and decreases the functions of mast cells and eosinophils.^{11–13} CsA inhibits eosinophil survival, cytokine secretion and recruitment of eosinophils to the sites of allergic inflammation.^{11–13} It also inhibits mast cell survival, secretory response, histamine release, prostaglandin production, and cytokine secretion.^{13,14}

CsA has been shown to inhibit canine and murine keratinocyte proliferation, reduce lipopolysaccharide-induced prostaglandin-E2 synthesis in canine and murine keratinocytes, and inhibit the production of chemokines (CXC chemokine KC and CCL2) in the murine keratinocytes.¹⁵ It has also been shown to significantly reduce the IFN- γ -induced production of IFN- γ -inducible protein 10 in human keratinocytes.¹⁵ All of these properties contribute to the antiinflammatory and immunomodulatory action of CsA in the treatment of allergic skin disease.¹⁵

PHARMACOKINETICS

The absolute oral bioavailability of CsA in dogs and cats is low and highly variable.² Oral bioavailability is higher in cats than in dogs, with a lower clearance and a slightly longer elimination half-life.¹⁶ The low bioavailability of CsA can be explained by the high molecular weight of the drug, its low water solubility, the effect of the P-glycoprotein efflux pump at the intestinal level, and metabolism by cytochrome P450 3A enzymes located in the small intestinal mucosa and liver.^{17–19} In dogs, the veterinary-labeled oral CsA is rapidly absorbed, but bioavailability is variable and can range from

23% to 45%.²⁰ Based on pharmacokinetic data in dogs, administration of CsA is recommended 2 hours before or after feeding, because its bioavailability decreases when given with food.¹⁸ The mean bioavailability of an ME CsA was reduced by 22% when administered to dogs with food, whereas the individual variability in drug absorption increased.¹⁸ Therefore, it is recommended that dogs be dosed on an empty stomach to optimize the drug's bioavailability. Even though there is an obvious effect of feeding on oral bioavailability, a small-scale study found that administration of CsA with food did not influence the clinical response in dogs.²¹ In cats, a pharmacokinetic study showed no consistent difference in the mean extent of drug absorption when administered orally to fed or starved cats or mixed in with food.⁶

Being lipophilic, CsA distributes widely in the tissues. The drug concentration in epidermis and dermis is about 10-fold higher than in the blood.²²

CsA is metabolized primarily by cytochrome P450, in particular CYP3A4, in the liver and small intestine.²³ P-glycoprotein is also associated with excretion of CsA, acting as a drug efflux pump that actively transports CsA back into the intestinal lumen.²³ The same cytochrome P450 enzymes (CYP3A4) are involved in both intestinal and hepatic metabolism.²⁴ As much as 50% of oral CsA metabolism may be attributed to intestinal metabolism.²³ Elimination is mainly biliary with minimal renal excretion in all species.²⁵

When applied epicutaneously, CsA has a poor skin penetration despite being lipid soluble; presumably this is related to the large molecular weight of the compound.^{2,26} In an abstract evaluating transdermal CsA, only 1/6 cats had blood levels that were considered to be therapeutic.²⁷

Effect of Bodyweight on Dosing

Because CsA is hydrophobic and concentrates in fat, some have proposed dosing patients based on their ideal body weight.²⁸ In humans, obesity does not significantly affect CsA pharmacokinetics.²⁹ In dogs weighing greater than 15 kg, a reduced CsA dosage (mean 4.4 mg/kg/d) was required to control symptoms when compared to dogs less than 15 kg.³⁰ A mean decrease of 0.04 mg/kg/d was found for every kilogram increase in body weight.³⁰

MONITORING BLOOD LEVELS OF CYCLOSPORINE

The most commonly used methods for measuring blood CsA levels include high-pressure liquid chromatography (HPLC), fluorescent polarization immunoassay (FPIA), and radioimmunoassay (RIA).² HPLC is time consuming and not cost-effective for routine practice. RIA and FPIA use antibodies that may cross-react with CsA metabolites, resulting in higher blood concentrations compared with HPLC.^{2,18} In dogs, CsA blood levels using FPIA were 1.5 to 1.7 times higher than when using HPLC.¹⁸ A trough concentration of 600 ng/mL has previously been established to attain sufficient immunosuppression to prevent organ rejection in canine transplant recipients.^{31,32} A study evaluating the pharmacodynamic effects of CsA using flow cytometry and cytokine expression concluded that T-cell function is suppressed at trough blood drug concentrations exceeding 600 ng/mL, and is at least partially suppressed in some dogs at lower dosages.¹⁰

Interpretation of CsA levels for treatment of atopic dermatitis is difficult because there is limited data correlating positive clinical responses with CsA blood levels. Clinical response to therapy is often the most reliable method of assessing efficacy with CsA therapy. Considering the large margin of safety of CsA in dogs, the variability of bioavailability, and the lack of correlation between blood concentrations and clinical response, routine monitoring of blood CsA is not currently recommended in dogs with

atopic dermatitis.¹⁸ The author typically only performs trough CsA levels if there is a lack of clinical response (before increasing dose) or if there is a concern for toxicity or superabsorption.

In cats, blood levels of CsA in field studies were highly variable, even among cats with similar clinical response, suggesting that correlations could not be generalized between cats with regard to blood CsA levels and clinical response.⁶ CsA levels pertaining to toxoplasmosis are discussed later.

DRUG INTERACTIONS

Numerous interactions have been reported between CsA and other drugs, mainly caused by the shared metabolic pathways involving cytochrome P450 (CYP3A4) and/or competition with P-glycoprotein.¹⁸ Drugs that inhibit cytochrome P450 decrease hepatic clearance of CsA, resulting in increased serum levels of CsA, whereas drugs that induce P450 activity can result in decreased blood concentrations of CsA.¹⁸ Common medications/treatments that may interact with CsA that have been studied in veterinary medicine are reviewed here.

Azole Antifungals

Azole antifungals are commonly used in veterinary dermatology to increase blood levels of CsA and save on associated costs. Ketoconazole is most commonly used for this purpose. Ketoconazole inhibits CYP3A and results in increased blood levels of CsA. Ketoconazole also inhibits P-glycoprotein, resulting in decreased transport of CsA into the intestinal lumen and higher bioavailability. Depending on the dose of ketoconazole administered, the total dose of CsA may be decreased by up to 75% to 90% in dogs.^{33,34} The extent of the interaction between ketoconazole and CsA is variable, and CsA blood concentrations are not predictable.² Individual dose adjustments may therefore be required. The author commonly uses a starting dosage of ketoconazole 5 to 10 mg/kg once daily combined with modified CsA 2.5 mg/kg once daily.

Unlike ketoconazole, which is mainly metabolized in the liver, fluconazole is primarily excreted unchanged in the urine.²⁰ Although fluconazole inhibits hepatic CYP3A *in vitro*, it seems to have no inhibitory effect on the P-glycoprotein encoded by MDR1.³⁵ Fluconazole has been shown to significantly increase the oral bioavailability of CsA and increase its blood concentration in healthy beagles.³⁶ Increased oral bioavailability of CsA after fluconazole administration in dogs is likely achieved by decreasing the first-pass effect that is associated with CYP3A, rather than P-glycoprotein activity during intestinal absorption of CsA.³⁶ The effect of fluconazole on the CsA dosage has also been investigated in renal-transplanted and normal dogs receiving CsA-based immunosuppressive therapy.³⁷ At first, CsA was administered orally twice daily to increase the blood trough level between 400 and 600 ng/mL. After the addition of fluconazole (5 mg/kg once daily), the CsA dosage was adjusted to maintain its therapeutic blood concentration.³⁷ Fluconazole significantly decreased CsA dosage in both normal and renal-transplanted dogs, but a higher dosage of CsA was needed in renal-transplanted dogs.³⁷ In normal dogs, the CsA requirements significantly decreased by 29% to 51% compared with initial CsA doses.³⁷

Metoclopramide

A recent article showed no effect of metoclopramide (0.3–0.5 mg/kg) on the pharmacokinetic parameters of CsA in healthy dogs.³⁸ An adjustment of the CsA dose may not be needed when metoclopramide is coadministered orally to prevent common adverse effects of CsA.³⁸

Cimetidine

Cimetidine is a potent inhibitor of hepatic microsomal enzymes.³⁹ In dogs, cimetidine may delay (but not decrease) absorption of orally administered CsA with no overall effect on the pharmacokinetics of CsA.³⁹

Grapefruit Juice

In human studies, grapefruit juice administered before oral administration of CsA enhances the blood concentration of CsA by 45% to 62%.^{40,41} Grapefruit juice contains furanocoumarins, which are inhibitors of intestinal (but not hepatic) CYP3A enzymes.^{42,43} Inhibition of CYP3A-mediated metabolism of CsA is the proposed main mechanism by which grapefruit juice increases CsA bioavailability.^{40,41} Powdered whole grapefruit (PWG) had the potential to reduce the required oral administered dose of CsA in dogs, but only when PWG was used in an amount of at least 10 g; this is currently not a cost-effective option.³⁸

St. John's Wort

St. John's Wort (SJW) is a herb that is known to induce cytochrome P450, and, in humans, is associated with decreased blood levels of CsA.⁴² In dogs, repeated administration of SJW affected the pharmacokinetic profiles (decreased maximum concentration and area under the curve) of CsA, presumably secondary to an increase in metabolism of CsA caused by upregulation of cytochrome P450 enzymes.⁴²

SIDE EFFECTS IN DOGS

In dogs, vomiting, diarrhea, and anorexia are the most commonly seen side effects. In a review of prospective clinical trials with CsA, vomiting (25% overall prevalence) and soft stools or diarrhea (15% overall prevalence) were the most commonly reported side effects.⁴⁴ Decreased appetite or anorexia was reported in 2% of the total adverse reactions.⁴⁴ In a different study, vomiting was reported in 31% of dogs receiving CsA at 5 mg/kg/d.⁴⁵ Of the dogs that vomited, 73% had less than 3 vomiting episodes during the 16-week trial; 10% had 4 to 7 episodes and 6% vomited once to twice weekly.⁴⁵ Diarrhea was reported in 20% of dogs, with most dogs only having a single episode.⁴⁵ Most gastrointestinal (GI) disturbances with CsA in dogs are observed early in the course of treatment and abate with time.⁴⁴

To help alleviate GI symptoms, the author commonly has owners freeze the CsA capsule for 30 to 60 minutes before administration and recommends administering the medication with a small amount of food. If this does not improve the vomiting, metoclopramide can be given 30 to 60 minutes before administration of CsA. Another medication that can be helpful in decreasing CsA-associated GI side effects is maropitant citrate (Cerenia; Pfizer Animal Health). The author has had good success using high-fiber supplements such as canned pumpkin and probiotics in dogs that develop diarrhea/soft stools on CsA. Zinc-carnosine and vitamin E supplementation (Gastric-Cal; Teva Animal Health) did not ameliorate GI side effects associated with CsA therapy.⁴⁶ In a small-scale study, giving CsA with food did not decrease the frequency of adverse events/side effects.²¹

Other adverse reactions reported in dogs with CsA therapy include:

- Gingival hyperplasia^{2,19,47}
- Cutaneous papillomatosis^{2,19}
- Hypertrichosis^{2,19}
- Psoriasiform lichenoid dermatosis⁴⁸

- Excessive shedding, increase in nail growth^{2,19}
- Hyperkeratosis of the footpads^{19,47}
- Seizures⁴⁷
- Shaking, trembling, or convulsions⁴⁷
- Urinary tract infections^{47,49}
- Behavioral changes including lethargy, hyperactivity, nervousness, restlessness, irritability, and light sensitivity⁴⁷
- Polyuria/polydipsia⁴⁷
- Pruritus after administration⁴⁷
- Cutaneous flushing⁴⁷
- Weight loss⁴⁷
- Lymphadenopathy⁴⁷
- Neoplasia: histiocytoma, lymphoma, mast cell tumor⁴⁷
- Disseminated nocardiosis in a dog with neurologic disease receiving CsA/ketoconazole for atopic dermatitis⁵⁰
- Multiple papillomavirus-associated epidermal hamartomas and squamous cell carcinomas in situ in a dog following chronic treatment with prednisone and CsA⁵¹

Most of these reported side effects are reversible with discontinuation of the CsA.

In a review of 9 dogs that developed hyperplastic skin growths on CsA, most dogs (7/9) had lesions that clinically and histopathologically were compatible with psoriasiform lichenoid dermatosis and 2/9 were positive for papillomavirus.⁴⁸ Psoriasiform lichenoid dermatosis is thought to be a reaction secondary to staphylococcal pyoderma; these cases typically completely respond to antimicrobial therapy.⁴⁸

Gingival hyperplasia (**Fig. 1**) is presumed to be secondary to CsA-mediated inhibition of collagen degradation and stimulation of fibroblast proliferation.⁴⁴

Based on evidence in humans, the author has used azithromycin-containing toothpaste to help control CsA-induced gingival hyperplasia in dogs.⁵² More severe cases may require dental treatments and surgical debulking.

Cutaneous papillomas in dogs receiving CsA are typically self-limiting once CsA is discontinued. Azithromycin 10 mg/kg once daily for 10 days can be prescribed to hasten resolution of the papillomas.⁵³ In the author's experience, CsA can often be restarted in these cases at a decreased dosing frequency without recurrence of papillomas.



Fig. 1. Gingival hyperplasia in a West Highland white terrier receiving CsA for atopic dermatitis.

Nephrotoxicity and hypertension are commonly reported in humans treated with CsA; however, this has not been shown in dogs, even when given at a dosage of 30 mg/kg/d for 90 days.^{43,46} Hepatotoxicity has also been reported in humans receiving CsA; safety studies have not reported this side effect in dogs.⁴⁴

Clinicopathologic Changes

Clinicopathologic abnormalities are reported in up to 25% of patients receiving long-term CsA.⁵⁴ Reported changes (with frequencies when available) include increased alkaline phosphatase, alanine aminotransferase, gamma-glutamyl transpeptidase, aspartate aminotransferase, creatinine (7.8%), hyperglobulinemia (6.4%), hyperphosphatemia (5.3%), hyperproteinemia (3.4%), hypercholesterolemia (2.6%), hypoalbuminemia (2.3%), hypocalcemia (2.3%), increased blood urea nitrogen (2.3%), hypernatremia, hyperkalemia, hypercalcemia and hyperchloremia; these changes were not typically associated with clinical signs of disease.^{47,54} Proteinuria has rarely been reported in dogs receiving CsA,⁴⁷ and urinary tract infections and hypertension should be ruled out in these cases.

A retrospective analysis of 87 dogs receiving CsA for greater than 5 months found that dogs in the CsA treatment group were significantly more likely to have a positive urine culture.⁴⁹ CsA-treated cases were divided into dogs receiving concurrent glucocorticoids and those receiving CsA alone. Dogs receiving CsA and glucocorticoids concurrently were significantly more likely than those on CsA alone to have a positive urine culture.⁴⁹ A prospective study is needed to further evaluate the risk of developing urinary tract infections in dogs treated with CsA.

Cautions/Contraindications

The safety and efficacy of CsA in dogs less than 6 months old or less than 1.8 kg are unknown.⁵ The drug is contraindicated for use in dogs with a history of malignant neoplasia and should not be given to breeding dogs and pregnant or lactating bitches.⁵ The long-term concurrent use of CsA with glucocorticoids should be avoided to prevent the development of potentially severe opportunistic infections.⁵⁵

Effect of CsA on Glucose Metabolism

After 3 weeks of CsA administration at 20 mg/kg, dogs remained normoglycemic, but retrieved islet tissue showed a significantly lower total insulin output than that of control animals.⁵⁶ In an article evaluating the effects of modified CsA at the labeled dose for atopic dermatitis, a disturbance of glucose metabolism was shown.⁵⁷ The fructosamine levels were significantly increased after treatment with CsA, although the disturbances were mild because no dogs had a fructosamine concentration after treatment that was more than the reference range.⁵⁷ Peak glucose concentrations were increased 20 and 30 minutes after a glucagon stimulation tests and the overall plasma glucose concentrations (based on areas under concentration-time curves before and after CsA treatment) were increased with CsA therapy.⁵⁷ Serum insulin levels were significantly lower following CsA treatment.⁵⁷ The mechanism for alteration in glucose metabolism is not fully understood, but has been theorized to involve reduced ability of islets to secrete insulin in response to a secretagogue stimulus.⁵⁷ The clinical significance of these findings is unclear because CsA is commonly used for the treatment of atopic dermatitis in dogs with diabetes mellitus.

In a study evaluating the effect of diabetes/hyperglycemia on CsA pharmacokinetics, diabetic dogs showed a significant increase in total body clearance of CsA compared with healthy dogs and a decrease in its biologic half-life (9.32 hours vs 22.56 hours).⁵⁸

SIDE EFFECTS IN CATS

Commonly reported adverse reactions in cats receiving CsA from 2 large field studies (total 205 cats) included⁵⁹:

- Vomiting, retching, regurgitation (35%)
- Weight loss (20%)
- Diarrhea (15%)
- Anorexia/decreased appetite (14%)
- Lethargy/malaise (14%)
- Hypersalivation (11%)
- Behavioral changes including hiding, hyperactivity, aggression (9%)
- Ocular discharge/epiphora/conjunctivitis (7%)
- Sneezing/rhinitis (5%)
- Gingivitis/gingival hyperplasia (4%)
- Polydipsia (3%)

Persistent, progressive weight loss that resulted in hepatic lipidosis occurred in 2 of 205 cats in field studies.⁵⁹ Close monitoring of body weight is recommended in cats during treatment with CsA.

CsA may increase the susceptibility to infection and the development of neoplasia.⁶ One of 205 field study cats died of the effusive form of feline infectious peritonitis.⁵⁹ In CsA safety studies, 1 cat receiving 5 times the approved dose developed lymphoma that was present in the kidneys and mesenteric lymph nodes on necropsy.⁵⁹ Cats treated with CsA after receiving kidney transplants had more than 6 times higher odds of developing posttransplant metastatic neoplasia (most commonly lymphoma) compared with control cats.⁶⁰

In a article evaluating side effects of 50 allergic cats receiving CsA, adverse events occurred in 66% of cats.⁶¹ Adverse events likely to be associated with CsA included vomiting or diarrhea within 1 to 8 weeks of receiving CsA (24%), weight loss (16%), anorexia and subsequent hepatic lipidosis (2%), and gingival hyperplasia (2%).⁶¹

Toxoplasmosis

Seropositivity for toxoplasmosis is widespread in the United States, with 31.6% of clinically ill cats being positive on immunoglobulin (Ig) M or IgG.⁶² Toxoplasmosis in association with CsA for feline atopic dermatitis has been previously reported in case reports.^{63,64} The reported clinical signs included respiratory symptoms and hepatic failure.^{63,64} The effect of CsA (label dose) on the *Toxoplasma gondii* status of cats when administered before and after infection with *T gondii* or only after infection with *T gondii* was recently evaluated.^{59,65} In the group that was treated with CsA before and after infection with *T gondii*, 2 cats developed disseminated toxoplasmosis.⁵⁹ Clinical signs typical for toxoplasmosis (GI symptoms, lethargy) were seen in most cats in the study, but resolved within 6 weeks following infection; clinical signs were more severe and lasted the longest in the group that was treated with CsA before and after infection.⁵⁹ CsA did not reactivate oocyst shedding or clinical disease/illness in cats previously exposed (seropositive) to *T gondii*.^{59,65,66} CsA increased the severity of *T gondii* infection in naive cats, but not in seropositive cats.^{59,65} Recrudescence of toxoplasmosis in seropositive cats receiving the labeled dose of CsA for atopic dermatitis is unlikely, but further data are needed to determine the risk; it is likely that potential for *T gondii* activation relates to CsA concentrations in individual cats.⁶⁶ *T gondii* is not cleared from the tissues of cats treated with clindamycin, potentiated sulfonamides, or azithromycin; therefore, the benefit of treating *T gondii*-seropositive cats before administration of CsA is unknown.⁶⁶

Seronegative cats with high CsA levels (typically >1000 ng/mL) are at the highest risk of developing acute fatal toxoplasmosis if they are newly exposed to the parasite.⁶⁶ Therefore it is critical that *T gondii*-negative cats treated with CsA avoid exposure. Methods to decrease exposure include keeping cats indoors, restricting any hunting behavior, and avoiding raw meats. If CsA is administered to cats that go outdoors (which the author does not recommend), monitoring CsA levels is strongly recommended.

Feline Herpesvirus 1 Infection

A recent abstract evaluated the effect of CsA and methylprednisolone on recrudescence of feline herpesvirus 1 (FHV-1) infection in cats with chronic herpesvirus infection.⁶⁷ Although clinical signs of activated FHV-1 occurred in some cats administered methylprednisolone or CsA, disease was mild/self-limiting and there was no significant difference in development of clinical signs between the treatment groups.⁶⁷

Clinicopathologic Changes

Reported clinicopathologic changes in cats receiving CsA at 3 times the label dose included mild increases of cholesterol, glucose, total protein, blood urea nitrogen, creatinine, and lymphopenia.⁶ Glucosuria was noted in 3 treated animals that also had hyperglycemia.⁶

Cautions/Contraindications

CsA should not be used in cats with a history of malignant disorders, suspected malignancy, and cats infected with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV).⁶ The safety and effectiveness has not been established in cats less than 6 months of age or less than 1.4 kg body weight.⁶ CsA is not labeled for use in breeding cats and pregnant or lactating queens.⁶ CsA is not labeled for use with other immunosuppressive agents.⁶

EFFECT OF CYCLOSPORINE ON VACCINATION

In a small study, 16 dogs received either 20 mg/kg daily of CsA or placebo for 56 days and were vaccinated on day 27 with a killed rabies vaccine and a multivalent distemper, hepatitis, leptospirosis, parainfluenza, parvovirus (DHLPP) vaccine (including modified live parvovirus).⁴⁷ Results revealed no antibody titer increase in any dog (including placebo/control dogs) to any of the components of the multivalent DHLPP vaccine, but appropriate antibody titer response in all dogs to the killed rabies vaccine by day 42.⁴⁷ Studies have not been performed at the therapeutic/approved dosing and it is unclear why dogs in the control group did not develop an increase in antibody titer.⁴⁷ Because of the drug's mechanism of action, the manufacturer recommends the use of killed vaccines in patients receiving CsA.⁵

Fully vaccinated (feline viral rhinitis, calicivirus, and parvovirus [FVRCP], rabies, FeLV) cats were administered CsA at 3 times the labeled dose.⁵⁹ Twenty-eight days into treatment, cats received booster vaccines for FVRCP, FeLV, and rabies, and were vaccinated for the first time with FIV.⁵⁹ Vaccine titers for previously administered vaccinations were decreased in the CsA-treated cats compared with controls, but remained adequate.⁵⁹ However, cats on CsA failed to develop titers to FIV vaccine.⁵⁹ Titer response to cats receiving 3 times the labeled dose of CsA depended on vaccination status before treatment; vaccine naive cats failed to develop titers when they were vaccinated while being treated with CsA.⁵⁹ Studies have not been performed at the labeled dose. The long-term effects of CsA on vaccine titers in dogs and cats remain unclear.

EFFECT OF CSA ON ALLERGY TESTING

CsA was found to have no significant effect on serum allergen-specific IgE levels and intradermal tests when administered at 5 mg/kg for 21 days to dogs with experimentally induced flea allergy dermatitis.⁶⁸ No significant effect was found on moderate and strong intradermal allergy test results in dogs before and after 42 days of treatment with CsA.⁶⁹ In a double-blinded, placebo-controlled study evaluating the effect of CsA (5 mg/kg once daily for 30 days) on intradermal and serum IgE allergy testing, CsA did not have a statistically significant effect on intradermal reactivity or serology results.⁷⁰

CSA AND ALLERGEN-SPECIFIC IMMUNOTHERAPY

The effect of CsA on allergen-specific immunotherapy (ASIT) has not been studied in dogs and cats. In the author's practice, CsA is commonly used both during the induction and maintenance phases of ASIT, with no perceived decrease in efficacy. In humans with atopic dermatitis, low-dose CsA has been shown to significantly increase the T-regulatory cell population.⁷¹ Success of allergen-specific immunotherapy in dogs has recently been shown to be associated with an increase in T-regulatory cell population, which regulates immune system homeostasis via production of cytokines such as IL-10.⁷² It is possible that the CsA may be synergistic with ASIT, but the interaction between CsA and ASIT requires further investigation.

DERMATOLOGIC USES/INDICATIONS

CsA has been used to treat a variety of inflammatory and immune-mediated dermatoses in dogs and cats.

Atopic Dermatitis in Dogs

The main indication for CsA in veterinary dermatology is for the treatment of atopic dermatitis. CsA is approved for use in dogs for the treatment of atopic dermatitis at the dosage of 5 mg/kg once daily.⁵ The International Task force on Canine Atopic Dermatitis 2010 practice guidelines concluded that there is good evidence for high efficacy of CsA at 5 mg/kg once daily in the treatment of dogs with atopic dermatitis.⁵⁵ Clinical improvement takes a minimum of 4 to 6 weeks, so no adjustment in dosing is recommended before 30 days of therapy.⁵⁵ In a systematic review and meta-analysis, 799 dogs in 10 studies had been treated with CsA (n = 622), placebo (n = 160), oral glucocorticoids (n = 24), or antihistamines (n = 23).⁴⁴ Dogs were treated from 2 weeks to 6 months and doses ranged from 2.5 to 5 mg/kg.⁴⁴ After 4 to 6 weeks of CsA (5 mg/kg once daily), a 40% decrease in skin lesions and at least a 30% decrease in pruritus were noted.⁴⁴ The percentage of dogs showing at least a 50% improvement in clinical signs increased from 20% to 60%, after 4 weeks of treatment and from 63% to 87% after 12 to 16 weeks of therapy.⁴⁴

In most of the evaluated studies, 40% to 50% of patients were able to have their dosage decreased to every other day; in 20% to 26% of dogs the dosage could be decreased to twice weekly after 14 to 16 weeks, and the remainder of dogs (approximately 25%) required once-daily treatment.⁴⁴ A significant difference in efficacy was noted in CsA compared with placebo; however, no significant difference was noted in CsA compared with glucocorticoids.⁴⁴ Overall, CsA had a good to excellent response in 65% to 76% of patients, with better responses noted in dogs receiving longer treatment regimens.⁴⁴

Using Generic Modified CsA for Atopic Dermatitis in Dogs

A recent article evaluated the efficacy of a commercially available human generic CsA product (Equoral; Teva Pharmaceuticals) for canine atopic dermatitis.⁷³ Lesion and pruritus scores were reduced similarly to prednisone, with a reduction of lesion scores of greater than or equal to 50% in 85% (generic CsA) and 100% (prednisone) of dogs, and a reduction in pruritus scores of greater than or equal to 50% in 77% and 86% of dogs treated with generic CsA and prednisone, respectively.⁷³

Allergic Dermatitis and Eosinophilic Granuloma Complex in Cats

CsA in cats is labeled for the control of feline allergic dermatitis as manifested by excoriations (including facial and neck), miliary dermatitis, eosinophilic plaques, and self-induced alopecia in cats.⁶ The approved dosage is 7 mg/kg once daily for a minimum of 4 to 6 weeks or until resolution of clinical signs.⁶ The author most commonly starts cats on 5 mg/kg once daily with good success.

Various studies have reported efficacy of CsA for cats with allergic skin disease, eosinophilic granuloma complex, and stomatitis.^{59,74,75} A placebo-controlled field study was performed in 217 client-owned cats with allergic dermatitis.⁵⁹ Cats in the treatment group had a 65% improvement in lesional score and a perceived owner success rate of 79%.⁵⁹ Following initial daily treatment period, the dose of CsA may be tapered by decreasing the frequency of dosing to every other day or twice weekly to maintain the desired therapeutic effect.⁵⁹ Frequency of administration was reduced to every other day in 70% of cats, and, after 4 additional weeks, 57% of cats could be reduced from every other day to twice-weekly administration.⁵⁹ In a controlled double-blinded study comparing the efficacy of CsA and prednisolone in feline atopic dermatitis, it was shown that CsA is an effective alternative to prednisolone therapy in cats with atopic dermatitis.⁷⁶

IMMUNE-MEDIATED SKIN DISEASES

CsA is a safe and effective immunosuppressive therapy for many immune-mediated skin diseases. Immune-mediated skin diseases for which CsA has been used include:

- Perianal fistulas^{34,77–81}
- Sebaceous adenitis^{82–85}
- Pemphigus foliaceus and erythematosus^{86–90}
- Juvenile cellulitis⁹¹
- Vesicular cutaneous lupus erythematosus⁹²
- Erythema multiforme^{2,19}
- Discoid lupus erythematosus
- Sterile nodular panniculitis⁹³
- Metatarsal fistulae¹⁹
- Granulomatous folliculitis and furunculosis⁸²
- Nasal arteritis/ulcerative dermatosis of nasal philtrum¹⁹
- Facial dermatitis in Persian cats⁹⁴
- Sterile granuloma/pyogranuloma syndrome¹⁹
- Immune-mediated adnexal targeting including mural folliculitis, alopecia areata in a dog,⁸² and pseudopelade in a cat¹⁹
- Cutaneous reactive histiocytosis⁹⁵
- Feline plasma cell pododermatitis
- Vasculitis and ischemic dermatopathy (See articles by Innera and Morris elsewhere in this issue)

Perianal Fistula

Many publications have documented the efficacy of CsA for the treatment of perianal fistulas.^{34,77–81} In a randomized placebo-controlled study of dogs with perianal fistulas, lesions of all CsA-treated dogs, but none of the placebo dogs, improved after 4 weeks.⁷⁷ Mean total surface area and mean depth decreased 78% and 62%, respectively, in the CsA group but increased 29% and 11%, respectively, in the control group.⁷⁷

The most effective therapeutic dosing regimen for perianal fistulas has yet to be established. In many studies, CsA was given twice daily but data from recent studies suggest that once-daily administration may be equally beneficial.^{34,78,79} In a study evaluating once-daily treatment of perianal fistulas, various dosages (1.5, 3.0, 5.0, or 7.5 mg/kg once daily) were compared.⁷⁸ After 13 weeks of treatment 6/24 dogs were in complete remission, 11/24 were controlled or improved, and 7/24 had failed to respond.⁷⁸ The response of the dogs given the highest dosage (7.5 mg/kg once daily) was significantly better than the response of the other groups.⁷⁸ Relapses were common after discontinuation of treatment.⁷⁸ In a similar study, CsA 5 mg/kg once daily was more effective at reducing the surface area and severity of perianal fistula lesions than 2 mg/kg once daily.⁷⁹

Concurrent use of ketoconazole and CsA has also been evaluated for the management of perianal fistulas.^{34,61} One study evaluated ketoconazole (10 mg/kg once daily) and CsA (1 mg/kg twice daily) for 16 weeks to treat dogs with perianal fistulas.³⁴ Ninety-three percent of dogs showed complete resolution of fistulas during the treatment period and 50% had no recurrence after 12 months.³⁴ A similar study evaluated oral CsA (initial dosage of 2.5 mg/kg twice daily in 8 dogs and 4 mg/kg once daily in 4 dogs) and ketoconazole (8 mg/kg once daily).⁸⁰ Clinical signs resolved in all dogs within 9 weeks and recurred in 5/8 dogs.⁸⁰ The cost savings with combination CsA/ketoconazole therapy varied between 36% and 71%.⁸⁰ Preoperative therapy with CsA or CsA/ketoconazole in dogs undergoing surgical correction of their perianal fistulas has also been shown to be beneficial at minimizing recurrence.⁸¹

The author most commonly uses CsA 5 mg/kg once daily as a monotherapy or CsA 2 to 4 mg/kg/d combined with ketoconazole 5 to 10 mg/kg once daily when treating perianal fistulas in dogs. Given the high recurrence rates when treatment is discontinued, the dosing interval is decreased to the lowest frequency that controls the symptoms. The author does not commonly perform CsA levels in patients with perianal fistulas receiving CsA because serum CsA concentrations have been shown to be unpredictable and do not correlate with clinical response in many cases.⁷⁹

Sebaceous Adenitis

CsA was first reported to be effective for granulomatous sebaceous adenitis in a miniature pinscher.⁸³ CsA (5 mg/kg once daily) significantly decreased clinical scores in dogs with sebaceous adenitis after 4 months of treatment and remained low after 8 and 12 months.⁸⁴ On histology, the severity of inflammation was significantly decreased with CsA treatment.⁸³ The percentage of hair follicles with sebaceous glands increased, suggesting regeneration of sebaceous glands.⁸³ Clinical signs recurred when CsA administration was discontinued.⁸⁴

A recent article compared the efficacy of CsA alone or combined with topical therapy with conventional topical therapy for sebaceous adenitis.⁸⁵ Topical treatment, both alone and in combination with CsA, reduced scaling more effectively than CsA alone.⁸⁵ Both therapies reduced alopecia. There was evidence of a synergistic benefit on both scaling and alopecia if both treatment options were combined.⁸⁵ Inflammation

of the sebaceous glands was also best reduced by a combination of both CsA and topical therapy.⁸⁵ Regeneration of sebaceous glands was best achieved by CsA, either given alone or in combination with topical treatment.⁸⁵

Pemphigus Foliaceus

CsA at a dosage of 5 and 10 mg/kg once daily was evaluated in 5 dogs with PF.⁸⁸ No cases achieved complete remission, and 4/5 dogs had to be withdrawn from the trial because of exacerbation of lesional scores.⁸⁸ CsA as a monotherapy at 5 to 10 mg/kg once daily cannot be recommended for the treatment of pemphigus foliaceus in dogs; however, higher doses have not been studied.⁸⁸ No studies exist on using CsA to manage feline pemphigus foliaceus, but the author has used CsA to manage several cases both as a steroid-sparing agent and as sole therapy.

CsA is more effective for canine pemphigus foliaceus when used in combination with other therapies.⁸⁷ In 3 dogs with pemphigus foliaceus already receiving azathioprine and glucocorticoids, oral CsA at 7.5 to 10 mg/kg/d was used with oral ketocozazole at 2.5 to 5 mg/kg/d to successfully induce remission.⁸⁹ CsA was used successfully with prednisone alone to induce remission of pemphigus foliaceus in 5 dogs.⁹⁰ Initial dosages ranged from 1 to 2.6 mg/kg/d for prednisone and 5 to 18 mg/kg/d for the CsA.⁹⁰ Although the initial CsA dosage was maintained in each patient, the prednisone dosage was then tapered to 0.5 mg/kg every other day with no relapse of signs.⁹⁰ The CsA was continued and eventually tapered to 3 to 4 mg/kg every other day.

MISCELLANEOUS DERMATOLOGIC CONDITIONS

Other dermatologic conditions reported to respond to CsA include:

- Follicular hyperkeratosis of cocker spaniels¹⁹
- German shepherd deep pyoderma¹⁹
- Primary seborrhea in springer spaniels, cairn terriers, and West Highland white terriers⁹⁶
- Chronic pedal furunculosis¹⁹
- End-stage proliferative external otitis in cocker spaniels and golden retrievers⁹⁷
- Feline urticaria pigmentosa⁹⁸

Table 1
Patient monitoring during cyclosporine therapy

Time	Recommended Monitoring
Before starting therapy	CBC, serum chemistry, urinalysis ± urine culture Physical and dermatologic examinations Body weight FeLV/FIV test (cats)
3 mo after starting therapy	CBC, serum chemistry, urinalysis ± urine culture Physical and dermatologic examinations Body weight
Every 6 mo during treatment	CBC, serum chemistry, urinalysis ± urine culture Physical and dermatologic examinations Body weight

Abbreviation: CBC, complete blood count.

PATIENT MONITORING DURING CYCLOSPORINE THERAPY

Table 1 shows the author's recommended patient monitoring during CsA therapy.

SUMMARY

CsA is a calcineurin inhibitor that is efficacious and approved for atopic dermatitis in dogs and allergic dermatitis in cats; it has also been used to successfully manage a variety of immune-mediated dermatoses. Drug interactions are commonly reported because of the shared metabolic pathways involving cytochrome P450 and/or competition with P-glycoprotein; ketoconazole can be used in clinical cases to reduce the oral required dosage and associated costs of CsA. Given the lack of correlation between blood concentrations and clinical response, CsA levels are not typically performed. The most commonly reported side effects caused by CsA are GI in nature; other reported side effects are typically reversible with discontinuation of CsA.

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