

Cyclosporin A: a new drug in the field of canine dermatology

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Abstract In the last few years, there has been growing interest in the use of cyclosporin to treat canine skin diseases. Cyclosporin exhibits potent immunomodulating properties that reflect its ability to block the transcription of cytokines genes in activated T lymphocytes. Cyclosporin also inhibits a number of immune allergic reactions that occur after activation of mast cells, Langerhans cells, eosinophils and keratinocytes. In randomized controlled trials, cyclosporin has proven to be as effective as glucocorticoids for treatment of canine atopic dermatitis at the inducing dosage of 5 mg kg⁻¹. The drug has also proven beneficial for the treatment of perianal fistulas in dogs. Other potential applications are suggested from small pilot open trials using dogs affected with various immune-mediated dermatological diseases. The pharmacokinetic properties of cyclosporin are very similar in dogs and man, but its safety margin is much wider in dogs. Therefore, routine cyclosporin blood level monitoring does not appear necessary. Although in man renal impairment and hypertension are often seen, even at low doses, these effects are not observed in dogs. Adverse reactions consist mainly of transient emesis and diarrhoea occurring during the first days of treatment. Other adverse reactions, such as gingival hyperplasia, verruciform lesions and hypertrichosis, appear to be dose-dependent, and occur rarely at therapeutic doses. An increased susceptibility to infections has not been reported in dogs receiving this drug.

Keywords: anal furunculosis, atopic dermatitis, canine, cyclosporin, dermatology, pharma-cokinetics, pharmacology.

INTRODUCTION

Cyclosporin A (CsA) is a compound isolated in the early 1970s from extracts of telluric fungi (*Tolypocladium inflatum gams*).¹ This drug has been used for its immunomodulating properties in humans after organ transplantation since 1977.² In human dermatology, CsA has been shown to be useful for the treatment of psoriasis³ and atopic dermatitis (AD).⁴ In canine dermatology, this drug has been the subject of growing interest over recent years for the treatment of perianal fistulae (PFi) and AD. Its efficacy has been explored in the treatment of other immune-mediated dermatoses.⁵ In addition, data have been accumulated on the pharmacokinetic and safety profiles of the drug in dogs. This review is aimed at summarizing the data available on the use of CsA for the treatment of canine skin diseases, with cross-reference to the human medical dermatology experience.

CLINICAL PHARMACOKINETICS

The pharmacokinetics of CsA in dogs and man are extremely similar. The bioavailability of the drug

administered orally as a vegetable oil-based formulation is in the range 20–27% in dogs^{6–11} and 25–35% in man.^{12,13} This relatively low bioavailability can be explained by the large molecular mass of the drug and its low water solubility. In addition, this drug is partially metabolized in the intestines by the cytochrome P450-dependent mono-oxygenase (CYP3A isoform) system.¹⁴ Absorption is also limited by P-glycoproteins that act as a drug efflux pump from the intestinal epithelial cells by transporting the drug from the intestinal cell to the lumen.¹⁵

In veterinary medicine CsA is available in micro-emulsion (ME) in soft gelatin capsules of 10, 25, 50 and 100 mg (Atopica®, Novartis Animal Health, Basel, Switzerland). In humans, CsA was first developed as a vegetable oil formulation of 100 mg mL⁻¹ offered as a drinkable solution or a soft gelatin capsules (Sandimmune®, Sandoz-Pharma, Basel, Switzerland) before the ME preparation became available. The ME formulation was designed to improve bioavailability. On contact with gastrointestinal fluids, this formulation readily forms a homogeneous monophasic microemulsion that mimics the mixed micellar phase of the standard formulation. Compared to the initial olive oil formulation, the ME is better absorbed. In man, the bioavailability of the ME formulation therefore increases from 20–30% to 30–40%.¹⁶ In dogs, the ME formulation offers a 35% bioavailability (Novartis AH data on file),

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Table 1. Mean pharmacokinetic parameters (SD) of cyclosporin A given intravenously to dogs

Reference	Dose (mg kg ⁻¹) [Number of dogs]	Sample	Analytical method	Clearance (mL min ⁻¹ kg ⁻¹)	T _{1/2} (h)	MRT (h)
Myre <i>et al.</i> ⁶	6 (N = 3)	Blood	HPLC	5.18 (1.92)	11.5 (1.8)	12.3 (3.00)
Gridelli <i>et al.</i> ⁷	5 (N = 5)	Blood	FPIA polyclonal	4.76 (1.95)	18.5 (4.6)	17.7 (3.1)
			HPLC	7.06 (0.87)	8.54 (0.73)	13.96
			RIA	4.40 (0.43)	16.2 (6.7)	
Buice <i>et al.</i> ⁸	20 (N = 6)	Serum	HPLC and RIA	8.11 (5.2)	29.4	–
White <i>et al.</i> ⁹	16 (N = 9)	Blood	RIA	3.66 (1.04)	17.5 (5.7)	10.7 (7.1)
Ritschel <i>et al.</i> ¹⁰	15 (N = 4)	Blood	FPIA	4.46 (1.10)	13 (4.9)	11.2 (4.1)
Takaya <i>et al.</i> ¹¹	2 (N = 13)	Blood	HPLC	7.09 (2.10)	5.06 (1.16)	6.6
D'Mello <i>et al.</i> ³⁰	4 (N = 5)	Blood	HPLC	7.0 (3.6)	8.7	9.5

HPLC: high-pressure liquid chromatography. RIA: radioimmunoassay. FPIA: fluorescence polarization immunoassay (TDx Abbott Diagnostics).

T_{1/2}: elimination half life. MRT: mean residence time. V_{ss}: volume of distribution at steady-state.

compared with 20–25% with the vegetable oil formulation.^{6–11} The ME formulation also decreases the inter-individual variability of drug absorption due to the increased absolute bioavailability and from the lack of effect of bile secretion on absorption. As a vegetable oil formulation, the absorption of CsA is very much influenced by bile secretion emulsifying the solution. In dogs, bile diversion results in a 75–80% decrease in drug absorption if given as vegetable oil formulation.^{11,17} As the bioavailability of CsA is not influenced by bile secretion when the drug is offered as ME the decrease of absorption after feeding is reduced in man.¹⁸ However, in dogs, even as ME formulation, the absorption is slightly delayed when the drug is given with food, and the individual variability is increased (Fig. 1). It is therefore recommended that the drug is administered either 2 h before, or after feeding. The clinical relevance of variations of blood concentrations when CsA is given with food during long-term treatment of canine skin diseases has not yet been determined.

In dogs and man, the drug is metabolized mainly in the liver and intestines. The same cytochrome P450 enzymes CYP3A4 are involved in both intestinal and hepatic metabolism.¹⁴ Hepatic metabolism of CsA tends to be three times more active in dogs than in humans¹⁹ but this is compensated for by a lower rate of metabolism in the liver than the intestine. With the liver playing a key role in the drug metabolism, it is not surprising that a 70% hepatectomy reduces the drug clearance rate by ≈ 50%, and thus increases the elimination half-life to the same extent.¹¹ However, as drug absorption is also reduced after hepatectomy, drug exposure is only increased by 20%.¹¹ Therefore, hepatic dysfunction is expected to impact minimally on the drug safety.

Despite the complex structure of CsA, the reactions involved in biodegradation of this molecule are limited to hydroxylations and demethylations, which results in ≈ 25 metabolites.^{20,21} It is generally accepted that the metabolites are devoid of pharmacological activity.²² Being lipophilic, CsA distributes widely in the tissues. The concentration of CsA in the skin is up to 10 times higher than blood concentrations in laboratory animals and man.^{23,24} In dogs, the same magnitude of the skin to blood concentration ratio has been found.²⁵

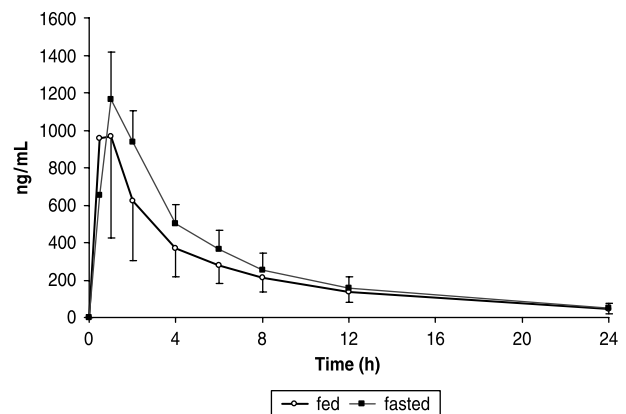


Figure 1. The feeding effect was tested in a cross-over study on eight beagles receiving each the gelatine capsule and the solution as ME formulation with or without food. The variability of the drug absorption was increased when the CsA ME was given with food. Very low levels were observed in 5 of the 16 dogs receiving the drug with food. Cyclosporin was analysed using fluorescence polarization immunoassay (TDx).

There is a low passage of CsA from blood to brain. In dogs, concentrations in the cerebrospinal fluid remain 10–100 times lower than in blood, even following repeated high-dose intravenous infusions.²⁶ Like ivermectin the ATP-binding transporters P-glycoproteins, especially the B1 cassette (Pgp, MDR1 gene product) play a major role in preventing CsA, from crossing the blood–brain barrier and accumulating in the brain.²⁷

When applied epicutaneously, CsA has a poor skin penetration despite being very lipid soluble.²⁸ In man, moderate to poor efficacy is obtained after topical application for treatment of AD.⁴ The poor skin penetration is suspected to be related to the high molecular mass of the compound. High lipophilicity may also slow the movement of the compound from the lipid-rich stratum corneum to the hydrated lower epidermis.²⁸ However, recent studies and anecdotal reports suggest that the topical application of CsA could be beneficial for treatment of PFI in dogs.²⁹

Elimination of CsA is mainly biliary with minimal renal excretion in all species (Table 1). The unchanged fraction of CsA eliminated by the kidneys is only 1–6% in dogs.²¹

Table 2. Comparison of pharmacokinetic parameters of cyclosporin A in dog and man after oral administration

		Cl (mL min ⁻¹ kg ⁻¹)	F (%)	T _{max} (h)	T _{1/2} (h)	MRT (h)
Dog ¹	Median	7	25*	1–2	8.6	10.9
	range	4–8	20–27		5–11	6.d–14
Man ²	Median or mean	4–10	30–40†	1–2	6–10	4–6
	range	2.5–11.6	8–60	–	2.9–15.8	–

Data obtained following the administration of vegetable oil based formulations and using an HPLC assay (excluding Ref. 8). ¹For references see text. ²References 12 and 13. Cl: clearance. F: absolute bioavailability. T_{max}: time of maximum concentration. T_{1/2}: elimination half-life. MRT: mean residence time. *Vegetable oil formulation. †Microemulsion formulation.

Table 3. Pharmacokinetic interactions with cyclosporin A

Effect of the concomitant therapy on CsA concentration	Well-documented report of interaction with marked effects on blood levels	Anecdotal reports of interaction	Documented evidence of absence of interaction
Increase of concentrations	<i>Ketoconazole</i> Fluconazole Itraconazole Diltiazem Erythromycin Clarithromycin Norfloxacin Phenytoin Metoclopramide <i>Vitamin E</i> ‡	Nafcillin Estradiol	
No change of concentrations			<i>Methylprednisolone</i> <i>Cimetidine</i> <i>Vitamin E</i> † Nonsteroidal anti-inflammatory drugs Fluoroquinolones* Beta Lactam antibiotics
Decrease of concentrations ¹	Trimethoprim sulphonamides	Clindamycin	

Text in italics: Interactions documented in dogs, in plain letters, interactions documented in man. Text in bold: increase or decrease by > 100% compared with to normal levels. Regular text: increase or decrease of 50–100% compared with normal levels.

*Except Norfloxacin; †with the CsA ME formulation (Atopica); ‡with the CsA vegetable oil formulation (Sandimmune).

In man: data from Campana *et al.*³⁴ review, in dogs see text.

BLOOD PROFILES AND PHARMACOKINETIC PARAMETERS

The pharmacokinetic parameters reported from several dog studies^{6–11,30} are presented in Table 2, and are compared with those observed in man.^{12,13} It can be noted that, in man, a wider variation of pharmacokinetic parameters occurs in comparison with dogs. This larger variability can be explained by the fact that many studies were conducted after organ transplantation (mainly liver or kidney), and these were likely to influence the pharmacokinetic parameters of the drug. Transplantation is followed by a reduction in absorption because of the increased activity of intestinal P-glycoprotein efflux pump as well as reduced bile secretion.^{31,32}

In man, it is recommended that the daily dose is divided into two administrations, in spite of the relatively slow elimination of the drug. High CsA peak concentrations are considered to be responsible for renal functional impairment.¹² In dogs, a once daily administration is preferred, because the drug's margin of safety is greater. This regimen is used for treatment of AD, but in most studies conducted on PFi, twice daily dosing was proposed. A recent study suggests that a single daily administration also yields satisfactory results in the treatment of PFi.³³

DRUG INTERACTIONS

In man, numerous interactions between CsA and other drugs occur because of shared metabolic pathways involving cytochrome P450 system (CYP3A4) and/or competition with the ATP-binding transporter P-glycoprotein (Table 3). P450-inhibiting drugs decrease hepatic clearance of CsA, increase its serum levels, and they could be responsible for toxic effects when very high blood concentrations are reached. However, P450 enzymatic inducers increase the hepatic metabolism of CsA, and thus decrease its blood concentration. Interactions have been investigated extensively in man, because of the relatively low margin of safety and the need to maintain a minimum trough level to prevent graft rejection.³⁴

Most of the drug interactions known in man have not yet been documented in dogs. In this species, interaction with ketoconazole is the most relevant, as it is often used to treat dermatological conditions. The clearance of CsA is decreased in the presence of ketoconazole, leading to higher CSA blood concentrations. The increase is proportional to the ketoconazole dose in the range 2–12 mg kg⁻¹.⁶ This interaction is clinically relevant as the daily dose of CsA can be markedly reduced.^{35,36} However, the extent of the interaction is

individually variable, and CsA blood concentrations cannot be predicted reliably. Individual dose adjustments are therefore required. Interaction with erythromycin, another drug used in veterinary dermatology, is well documented in man but not in the dog. Other macrolide antibiotics such as lincomycin or clindamycin are not known to interfere with CsA in man.³⁴

The interaction between CsA and cimetidine, a type-2 histamine receptor antagonist, has recently been evaluated in dogs.³⁷ Cimetidine, a potent inhibitor of the hepatic microsomal enzymes, delayed but did not decrease the absorption rate of CsA. Recently, water-soluble vitamin E polyethylene glycol succinate has been reported to enhance CsA bioavailability administered as vegetable oil formulation but not as ME formulation.³⁸ Water-soluble vitamin E is believed to improve bioavailability by micelle formation enhancing the absorption in the intestine.

An interaction between methylprednisolone (1 mg kg^{-1}) and CsA (20 mg kg^{-1}) was not found when both drugs were administered concurrently (Novartis Animal Health: data on file).

Most interactions due to transiently administered medications inducing a small increase in CsA blood concentrations are believed to be of no clinical relevance in dogs as CsA is not nephrotoxic.

MONITORING BLOOD CYCLOSPORIN LEVELS

The monitoring of CsA blood levels following organ transplantation has been established as a routine practice in human medicine. Blood monitoring initially was justified by the large individual variability of the drug blood levels, but was also useful to ensure the success of organ transplantation with minimal adverse reactions. In man, the relatively small margin of safety and the higher inducing dose require a careful dose adjustment. The minimum trough levels to be maintained for transplant success and minimal renal impairment have been evaluated in a large number of studies.³⁹

The relationship between blood concentration and efficacy has not been established for the treatment of psoriasis in man.⁴⁰ In a study in which the relationships among efficacy, dose, trough levels and area-under-the-curve (AUC) were analysed,⁴¹ a better correlation was found between efficacy and AUC than between efficacy and trough levels. A recent systematic review of clinical studies conducted in patients with psoriasis concludes that trough levels are not even useful for monitoring the level of renal impairment.⁴² In dogs, a minimum trough level required for efficacy in PFI is recommended by some authors, but these values are based on data established for human and animal patients receiving organ transplants. In addition, trough levels established in human medicine are 12 h concentrations as the drug is administered twice a day, but 24 h trough levels should be established for dogs when the drug is given once daily. At this time, a relationship has not

been established between CsA trough concentrations and efficacy for treatment of PFI^{33,35} or AD (Novartis Animal Health: data on file).

As the dose used in the treatment of AD is lower than that prescribed for prevention of organ transplantation rejection in humans, and because of the larger safety margin in dogs, trough-level monitoring does not appear to be justified in routine practice. Blood level measurements could be useful, however, when the drug is combined with ketoconazole, or with any other drug known to interfere with CsA metabolism, for long-term co-administration.

As the high-pressure liquid chromatography (HPLC) method is used often in laboratory studies, it is of limited value for clinician as it is expensive and time-consuming. Faster and simpler methods have been developed such as a fluorescent polarization immunoassay (FPIA commercially marketed as TDx by Abbott Laboratories, IL, USA) or radioimmunoassay (RIA, commercially marketed as CYCLO-Trac, INCSTAR Corp., Stillwater, MN, USA). However, these two assays employ antibodies that cross-react with some CsA metabolites⁴³ and therefore yield higher blood concentrations of CsA than HPLC.⁶ In dogs, blood concentrations measured by TDx assay are ≈ 1.8 times higher than those measured with HPLC assay.

MODE OF ACTION

CsA acts on different cells, but its main therapeutic action is on T lymphocytes. Cyclosporin induces rapidly reversible immunosuppression by inhibiting the initial antigen triggered activation phase of CD4⁺ T lymphocytes. This immunosuppression comes from the blocking of the transcription of genes encoding several cytokines, in particular interleukin (IL)-2. The molecular mode of action involves the specific binding of CsA to an intracellular protein, cyclophilin-1, belonging to the immunophilin family. Then the cyclophilin–CsA complex thus formed inhibits calcineurin, which is an enzyme involved in the nuclear translocation of the cytoplasmic component of NF-AT, an essential transcription factor of the IL-2 gene.⁴⁴ The absence of IL-2 synthesis prevents the activation and the proliferation of T lymphocytes in addition to the secondary synthesis of other cytokines, including IL-4, interferon (IFN)- γ and GM-CSF.^{45,46}

The immunomodulatory properties of CsA have been extensively investigated in rodents and man. Cyclosporin inhibits skin mast cell counts,⁴⁷ mast cell survival,⁴⁸ mast cell secretory response after stimulation,⁴⁹ mast cell histamine release^{50,51} and the secretion of cytokines IL-4, IL-5, tumour necrosis factor (TNF), IL-3 and IL-8.^{52–54}

Cyclosporin A inhibits eosinophil survival,⁵⁵ release of toxic granules,^{56,57} cytokine secretions⁵⁸ and recruitment to the sites of allergic inflammation.⁵⁹

Cyclosporin A decreases the number of epidermal Langerhans cells and inhibits the lymphocyte-activating

functions of these antigen-presenting cells.^{60–63} Cyclosporin A also reduces the cytokine secretion by keratinocytes.⁶⁴

Finally, CsA inhibits IgE and mast cell-dependent cellular infiltration at the sites of cutaneous inflammation by preventing TNF-mediated late-phase reactions in man and dogs. These findings have been corroborated by the demonstration that CsA reduces the severity of allergen-induced, late-phase, asthmatic response.⁶⁵

In dogs, few studies have been conducted, but it is likely that more information will be generated over the next years. In dogs, as in man, it was found that CsA also inhibits T-lymphocyte activation^{66,67} and cytokine production. Mast cell histamine release is also reduced following CsA incubation.⁶⁸

Cyclosporin A does not inhibit the secretion of IgA, IgG and IgM in dogs⁶⁷ as is the case in other species. It is well recognized that CsA does not alter humoral immunity. Cyclosporin A had no significant effect on serum allergen-specific IgE levels and intradermal tests when administered at 5 mg kg⁻¹ for 21 days to dogs with experimentally induced flea allergy dermatitis.⁶⁹ In another study evaluating the effect of high-dose CsA (20 mg kg⁻¹) on vaccination in dogs, no effect on vaccinal antibody titres could be found (Novartis Animal Health, data on file). Cyclosporin treatment should not interfere with vaccination as long as the protection is obtained mainly via a humoral response.

Cyclosporin A also has nonimmunological effects on nonimmunological cells.⁷⁰ *In vitro*, at a concentration of 1–10 µg mL⁻¹, CsA reversibly inhibits the proliferation and synthesis of normal and neoplastic keratinocyte DNA. This antiproliferative activity plays a major role in the treatment of psoriasis, which is a disorder characterized by epidermal hyperproliferation. Cyclosporin A has been also shown to induce the synthesis of tumour growth factor (TGF)-β that stimulates cells to increase their extracellular matrix deposition and decreases the production of degrading proteases, therefore inducing a fibrogenic state.⁴⁵ TGF-β secretion is probably responsible for the renal fibrosis observed in rats and man, and the gingival hyperplasia and verruciform lesions occasionally seen in dogs. The increased secretion of TGF-β could also contribute to the skin healing process, which in contrast to glucocorticoids is not inhibited by CsA.⁷¹

SAFETY

In dogs, the safety profile of CsA is now well documented through toxicological⁷² and safety studies in this species (Novartis Animal Health; data on file). Moreover, the safety profile of the drug has been established in recent controlled clinical studies that included more than 200 dogs treated for up to 4 months.^{33,35,36,73–76}

In contrast to similar pharmacokinetics existing between dogs and humans, the safety profile of CsA is different between the species. Nephrotoxicity and

increased blood pressure are the most troublesome side effects in humans.^{77–79} The mechanisms involved in the induction of nephropathy and increased blood pressure are complex. Cyclosporin is responsible for renal arteriolar vasoconstriction causing a reduction in kidney blood flow and glomerular filtration rate.⁸⁰ Vasoconstriction of the afferent artery results from endothelin and thromboxane release and activation of the rennin–angiotensin–aldosterone system.⁸¹ Primary renal impairment is therefore secondary to modifications of intrarenal haemodynamics. Hypertension also seems to be induced by other mechanisms such as an increased activity of the sympathetic nervous system⁸¹ the inhibition of nitric oxide and an increase in intracellular Ca²⁺ leading to vascular reactivity to vasoconstrictors agents.⁸² More recently, it has been suggested that nephrotoxicity could result from the inhibition of the adaptive responses to hypertonicity that occurs during the urine concentration mechanism.⁸² Prolonged treatment with CsA is associated with chronic renal damage because of reversible lesions of the renal parenchyma. In the long term, proximal tubular lesions can develop.⁸³

In dogs, pharmacological studies conducted with high-dose CsA (20–30 mg kg⁻¹) show only moderate renal effects, such as a reduction of the rate of urine flow and a reduction of sodium excretion, all without changes in renal clearance.^{84,85} Moreover, in toxicological studies conducted in dogs, signs of nephrotoxicity have not been noted clinically or histologically, even at the high dosage of 45 mg kg⁻¹ given for 52 weeks.⁷² This finding has been confirmed in safety studies employing dosages up to 33 mg kg⁻¹ for 90 days (Novartis Animal Health; data on file), as well as in clinical studies.^{74–76} None of the clinical trials revealed increases in blood creatinine levels. Therefore, it appears that the dog is much less sensitive than other species, such as rats or man, to the kidney-damaging effect of CsA. Such variation in the toxic effects of this drug could be explained by the excretion of intracellular CsA from the tubular cells by P-glycoprotein,⁸⁶ thereby preventing toxic effects, and/or by the absence of effect of CsA on calbindin D protein.⁸⁷ In man and rats, the concentration of this protein in kidney tubular cells decreases during treatment with CsA, which results in calcium accumulation and tubular cell dysfunction.⁷⁸ In dogs, this protein function is not inhibited.⁸⁷

Studies conducted with isolated arteries show increased blood pressure in dogs when high doses of CsA are perfused,⁸⁸ but in intact dogs, the oral administration of CsA at dosages of up to 33 mg kg⁻¹ for 90 days did not induce any change in systemic arterial blood pressures (Novartis Animal Health; data on file). The absence of effect on haemodynamic parameters is confirmed in other studies in which the mean arterial blood pressure⁸⁴ or systemic vascular resistance and cardiac output were measured.⁸⁹ It is suspected that the rennin–angiotensin–aldosterone system could be less responsive to the effect of CsA in dogs compared to man or rats.

An increase in the activity of plasma liver enzymes is reported as a common adverse reaction following CsA administration in man. In contrast, hepatotoxicity has not been observed in any of the safety studies or clinical trials in the canine species.^{72–76}

The most frequently observed adverse reactions in dogs in both toxicological and clinical studies were digestive signs, such as vomiting and diarrhoea. In clinical trials, vomiting occurred in 14–42% of the dogs, mainly in the early phase of the treatment, it appeared intermittently and was of short duration. Diarrhoea, which was observed in 16–18% of the dogs, occurred more frequently but for short periods at the initiation of treatment.

Other adverse drug events are reported in both dogs and man. Cutaneous and mucosal effects, such as gingival hypertrophy and hypertrichosis, are observed in at least 2% of human patients, and they are reversible upon cessation of CsA administration.⁷⁹ In dogs, swelling of the gums is rarely seen at the doses employed. This anomaly occurred only in 3% of the dogs in one clinical study,⁷⁶ and it was mostly seen in subjects treated with higher dosages.⁷² Gingival hyperplasia is reversible within a few weeks of discontinuation of administration.⁹⁰ It is hypothesized that such hyperplasia is caused by CsA-mediated inhibition of collagen degradation due both a stimulation of fibroblast proliferation⁹¹ and low collagenase expression.⁹²

Papilloma-like skin lesions have also been reported in dogs receiving CsA at high dosages (30–45 mg kg⁻¹) during safety and toxicological studies,^{72,93} but it was reported only in one dog given CsA at the therapeutic dose.⁷⁴ In none of these cases did histology, immunohistochemistry,^{69,71,83} electron microscopy⁶⁹ or polymerase chain reaction⁹⁴ permit the identification of any papillomavirus.

In dogs, there is no evidence of an increased frequency of infections during CsA therapy when given either for treatment of PFI or AD. In one study comparing CsA with glucocorticoids for treatment of canine AD, the frequency of bacterial skin infections was found to be lower, albeit not significantly, in dogs receiving CsA compared with those treated with methylprednisolone.⁷⁶ A 6-day course of 3.5 mg kg⁻¹ of CsA and glucantime in dogs with leishmaniasis was well tolerated without worsening of the clinical signs of this disease.⁹⁵ Similarly, in man, there has been no reports of diseases associated with bacterial infections in patients administered CsA for AD or psoriasis. The risk of opportunistic infections and lymphomas in these patients seems to be low, compared with that observed in transplant-receiving patients. This is probably because doses prescribed for skin diseases are lower than those used for prevention of rejection of organ transplants, and also because CsA is rarely, if ever, combined with other immunosuppressing drugs for treatment of dermatological diseases.⁹⁶

CsA stimulates hair growth, probably by inducing the hair follicle anagen phase.⁹⁷ This reversible effect is the cause of the hypertrichosis observed in human

subjects receiving CsA during transplantation immunosuppression. This effect has led to therapeutic trials in alopecia areata and in androgenic alopecia in humans.⁹⁸ In dogs, hypertrichosis is rarely reported, but hair shedding has been observed sometimes in clinical trials,⁹⁹ probably because of new shafts pushing out old ones. The molecular mechanisms of the CsA action on epithelial cells are not well elucidated.

Cyclosporin has been shown to inhibit insulin secretion in *in vitro* tests¹⁰⁰ and *in vivo* in glucose-stimulation tests.^{101–103} The inhibition is dose-dependent and well correlated with CsA blood levels. However, dogs eating normal diets remain normoglycaemic when receiving CsA even at 20 mg kg⁻¹ for 3 weeks.¹⁰⁴ In toxicological and target animal safety studies (Novartis Animal Health: data on file) and in clinical trials, glycaemias also remained within normal values.^{72,74–76}

In summary, results from toxicological, safety and clinical studies do not provide evidence to recommend the routine performance of biochemistry and haematology tests in the absence of signs suggesting any alteration of the physical condition.

The safety of long-term administration of CsA in dogs is not yet well documented. However, in a recent retrospective study,¹⁰⁵ a trend for an increased incidence of adverse reactions over time was noted in dogs receiving CsA for 6–30 months. Further studies are required on a larger population.

INDICATIONS

In canine dermatology, CsA is used for treatment of immune-mediated dermatoses, especially AD and Pfi.

Canine atopic dermatitis

Several clinical studies^{73–76} have established the activity of CsA for the treatment of AD in dogs. All trials have been recently analysed¹⁰⁶ in a systematic review of the pharmacotherapy of canine AD. It was concluded that all trials provided good evidence of the high efficacy of CsA administered at 5 mg kg⁻¹ once daily for up to 16 weeks (Table 4, Fig. 2). A reduction in pruritus and skin lesions was seen after 4 weeks of treatment. In half of the dogs with AD, the dose could be tapered after 4 weeks to every-other-day administration, followed later in some patients by twice-a-week dosing. Tapering the dose by increasing the intervals between administrations or decreasing daily doses appears to yield similar responses.¹⁰⁷ However, increasing the intervals between doses is likely to be associated with higher compliance from dog owners.

Two studies compared CsA with glucocorticoids.^{74,76} Both medications resulted in a similar improvement in skin lesions and pruritus. The median or mean reduction from baseline of lesion score was 58 and 69% in CsA- and glucocorticoid-treated dogs, respectively, in one study,⁷⁴ and 52 and 45% in the other.⁷⁶ Similarly, the reduction in pruritus score was 78 and 81% in the first study and 36 and 33% in the second. The lower

Table 5. Clinical response in dogs with anal fistula treated with CsA

Reference	Study design	Dose, frequency of administration and duration	No. dogs	Results
108	Uncontrolled	CsA 7.5–10 mg kg ⁻¹ twice daily 20 weeks	9	Improvement after one week in 9/9 (100%) dogs Complete resolution after 20 weeks Remission for 6 to over 18 months after treatment cessation
99	Randomized, blinded, placebo controlled Uncontrolled study following the placebo controlled study	CsA 10 mg kg ⁻¹ or placebo twice daily 4 weeks CsA 10 mg kg ⁻¹ b.i.d. 16 weeks	10 per group 20	All dogs improved under CsA, none under placebo Surface area decreased by 78%, depth by 62% under CsA; increase of these parameters under placebo Total resolution in 17/20 (85%) dogs, 3/20 improved Recurrence in 7/17 (41%) of dogs following treatment cessation
109	Uncontrolled	CsA 7.5 mg kg ⁻¹ twice daily 10–20 weeks	6	Lesion reduction by 50–90% within one week, gradual healing over 10–20 weeks Recurrence in one dog within 8 weeks following treatment cessation
110	Uncontrolled	CsA 4 mg kg ⁻¹ twice daily until resolution (mean 9 weeks)	26	Improvement in 25/26 (96%) dogs, complete remission in 18/26 (72%) dogs
33	Randomized, dose titration	CsA 1.5, 3, 5 or 7.5 mg kg ⁻¹ once daily for 13 weeks	6 per group	Faster clinical improvement in the dogs receiving 7.5 mg kg ⁻¹ than lower doses. Higher complete resolution rate at the highest dose (4/6) as compared to lower doses (2/18). Longer remission (> 12 months) in dogs treated for longer than 13 weeks No consistent relationship between CsA blood levels and efficacy
111	Randomized Dose titration	CsA 2 or 5 mg kg ⁻¹ once daily for 8–12 weeks. Low dose increased after 8 weeks is insufficient response	10 per group	Significant Improvement of lesions obtained with both doses. Complete resolution of lesions in 7/10 dogs receiving 5 mg kg ⁻¹ , and complete resolution of clinical signs in 8/10 dogs after 12 weeks. Dose increased to 5 mg kg ⁻¹ after 8 weeks in 6/10 dogs receiving 2 mg kg ⁻¹ Complete remission is 8 times more likely with the high dose compared to low dose Faster resolution of lesions with 5 mg kg ⁻¹ compared to 2 mg kg ⁻¹ , but 2 mg kg ⁻¹ sufficient for clinical signs improvement
35	uncontrolled	CsA 1 mg kg ⁻¹ Once daily ketoconazole 10 mg kg ⁻¹ once daily 16 weeks	16	Complete clinical remission in 14/16 dogs (93%) Remission for one year in 50% of the dogs
36	uncontrolled	CsA 2.5 mg kg ⁻¹ twice daily or 4 mg kg ⁻¹ once daily and ketoconazole 8 mg kg ⁻¹ once daily	8 6	Resolution of clinical signs resolution within 9 weeks but recurrence in 5/9 dogs

recurrence of lesions was present in five of eight dogs. The cost reduction of this combined therapy compared with that of CsA monotherapy varied between 36 and 71%. The concurrent administration of ketoconazole required dose adjustment, as there was a large individual and temporal variation in CsA blood levels.

The administration of CsA, alone or combined with ketoconazole, even in dogs in which PFI were not completely healed, appeared to be beneficial because the surgical procedures that were required were less extensive than those that would have been necessary without CsA pretreatment.

OTHER POTENTIAL APPLICATIONS, A LOOK FORWARD

The full potential of CsA benefit in canine dermatology has not been fully explored yet. A number of pilot studies or anecdotal observations suggest that CsA could be of interest in a number of diseases. Further research is warranted to investigate these potential uses.

Granulomatous sebaceous adenitis

Treatment with CsA could offer an alternative in the treatment of cases of granulomatous sebaceous adenitis (GSA) refractory to conventional therapy with retinoids. Cyclosporin at 5 mg kg⁻¹ twice daily was used for treatment of GSA in a dog.¹¹² A good response was obtained within 3 weeks with new hair regrowth and decrease of scaling severity. Examination of post-treatment skin sections confirmed the resolution of sebaceous and perifollicular granulomas and the decrease of hyperkeratosis. Adverse drug events were not reported.

Pemphigus foliaceus

The first report using CsA in vegetable oil for treatment of three dogs with pemphigus foliaceus (PF) was published in 1989.¹¹³ Good to complete resolution of lesions was obtained within 4–6 weeks in two dogs receiving 25 mg kg⁻¹. In one dog given 15 mg kg⁻¹ a temporary reduction in clinical signs was observed, but lesions did not respond to higher doses when the severity of the disease worsened.

Recently, a pilot study described the results of induction of treatment with ME CsA at a dosage of 5 then 10 mg kg⁻¹ once daily in five dogs with PF.¹¹⁴ The administration of CsA was unable to lead to complete remission in any of the enrolled subjects. Moreover four of five dogs entered in this trial had to be withdrawn because of exacerbation of lesional scores. Consequently CsA, at these proposed dosages, cannot be recommended for therapy of PF in dogs. However, it cannot be excluded that higher dosages of CsA could be more effective than those employed in the studies described herein. Future trials should also investigate whether CsA would be a useful adjuvant medication, helping lowering the dose of glucocorticoids when

both drugs are administered concurrently during the induction phase of immune-suppression.

Cutaneous lupus

Nonmicroemulsified CsA, given at 30 mg kg⁻¹ once daily, was used to treat successfully one dog with nasal cutaneous lupus.¹¹³ A good response was obtained after six weeks.

Generalized idiopathic sterile nodular panniculitis

CsA was used in two dogs with generalized idiopathic sterile nodular panniculitis.¹¹⁵ The dogs were treated with CsA at 5 mg kg⁻¹ orally, once daily. Within 2 weeks, there was an 80% reduction in the severity of skin nodules, and the dogs became afebrile. Treatment was continued for another 3 weeks and lesions were completely resolved by the end of 6 weeks of treatment. Cyclosporin was continued on an alternate day regimen for 1 month. Relapses were not noticed even after 8 months following the end of treatment.

Epitheliotropic lymphoma

A noticeable response was not observed in two dogs with epitheliotropic lymphosarcomas treated with CsA at 15 mg kg⁻¹ twice daily.¹¹³

OTHER POSSIBLE FUTURE USES

Some anecdotal uses of CsA for treatment of animal skin diseases have been recently reported.⁵ These dermatoses included chronic pedal furunculosis, erythema multiforme, follicular hyperkeratosis of cocker spaniels, German shepherd dog deep pyoderma, metatarsal fistulae, sterile pyogranulomatous syndrome and ulcerative dermatosis of the philtrum of Saint Bernard and Newfoundlands. In the springer spaniel, cairn terrier and West Highland white terrier successful treatment of primary seborrhea was recently mentioned.¹¹⁶ Finally, a pilot study indicated that CsA could be effective in end stage proliferative external otitis in cocker spaniel and golden retriever.¹¹⁷

However, recommendation of use of CsA for treatment of such diseases must await detailed publications of treatment efficacy, preferably based on results of prospective randomized controlled trials.

CONCLUSIONS

The increasing number of clinical trials and case reports provides evidence that CsA is a beneficial molecule to treat selected immune-mediated canine skin diseases. Its usefulness in man is limited by the frequency of adverse reactions such as nephrotoxicity and increased blood pressure, but luckily these effects are not seen in the canine species. Additional studies are required to fully explore the therapeutic potential of this medication. Nevertheless, CsA represents a good therapeutic alternative to the administration of

glucocorticoids due to its similar range benefit but lower risk of serious harm.

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Eric Guaguère has no direct financial interest/relationship with Novartis Animal Health other than consulting activities, however, the generation of this article was not included in such activities. Jean Steffan is employed as Development Manager at Novartis Animal Health, Basel, Switzerland. Thierry Olivry has no direct financial interest/relationship with Novartis Animal Health other than consulting activities. Contribution to the writing of this article was not included in paid consulting activities. Additionally, Novartis sponsored grants at NC State University in support of some of Dr Olivry's previous research projects.

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Résumé Ces dernières années, un intérêt grandissant a été noté pour l'utilisation de la ciclosporine dans le traitement de dermatoses canines. La ciclosporine présente des propriétés immunomodulatrices puissantes, qui sont liées à sa capacité à bloquer la transcription de gènes de cytokines dans les lymphocytes T activés. La ciclosporine inhibe également un grand nombre de réactions allergiques qui surviennent après activation des mastocytes, des cellules de Langerhans, des éosinophiles et des kératinocytes. Dans des essais randomisés et contrôlés, la ciclosporine s'est révélée aussi efficace que les glucocorticoïdes pour le traitement de la dermatite atopique canine à la dose d'induction de 5 mg kg⁻¹. La molécule s'est également avérée efficace pour le traitement des fistules périanales chez le chien. D'autres applications potentielles dans des maladies immunologiques variées sont suggérées par des études pilotes. Les propriétés pharmacocinétiques de la ciclosporine sont très similaires chez le chien et l'homme, mais la marge de sécurité est beaucoup plus importante chez le chien. C'est pourquoi la mesure des concentrations plasmatiques de ciclosporine ne s'impose pas en routine chez le chien. Alors que chez l'homme une insuffisance rénale et une hypertension sont souvent notées, même à des doses faibles, ces réactions ne sont

pas observées chez le chien. Les effets secondaires dans cette espèce consistent principalement en des vomissements et des diarrhées transitoires pendant les premiers jours de traitement. Les autres effets secondaires, comme l'hyperplasie gingivale, l'apparition de lésions verruqueuses et l'hypertrichose semblent dose-dépendantes, et surviennent rarement aux posologies usuelles. Une susceptibilité accrue aux infections n'a pas été rapportée chez les chiens recevant cette molécule.

Resumen En los últimos años ha habido un creciente interés en el uso de la ciclosporina para el tratamiento de enfermedades cutáneas caninas. La ciclosporina presenta propiedades inmunomoduladoras potentes que muestran su capacidad de bloquear la transcripción de los genes de citoquinas en linfocitos T activados. La ciclosporina también inhibe algunas reacciones inmunológicas alérgicas que se producen tras la activación de mastocitos, células de Langerhans, eosinófilos y queratinocitos. En pruebas clínicas controladas, al azar, la ciclosporina ha mostrado ser tan efectiva como los glucocorticoides para el tratamiento de la dermatitis atópica canina a una dosis inductiva de 5 mg kg⁻¹. El fármaco ha sido también beneficioso para el tratamiento de las fistulas perianales en perros. Se sugieren también otras aplicaciones potenciales en pruebas clínicas abiertas utilizando perros afectados por diferentes enfermedades dermatológicas inmunomediadas. Las propiedades farmacocinéticas de la ciclosporina son muy similares en perros y en humanos, pero su margen de seguridad es mucho más amplia en perros. Así, la monitorización rutinaria de los niveles sanguíneos de ciclosporina no parece ser necesaria. Mientras en humanos se producen con frecuencia afecciones renales e hipertensión, incluso a dosis bajas, no se observan estos efectos en perros. Las reacciones adversas consisten principalmente en emesis temporal y diarrea durante los primeros días del tratamiento. Otras reacciones adversas, como la hiperplasia gingival, las lesiones verruciformes y la hipertrichosis, parecen ser dosis-dependientes, y se producen raramente a dosis terapéuticas. No se ha observado una mayor susceptibilidad a las infecciones en perros que reciben este fármaco.

Zusammenfassung In den letzten Jahren gab es wachsendes Interesse an dem Einsatz von Cyclosporin zur Behandlung von Hauterkrankungen beim Hund. Cyclosporin zeigt beeindruckende immunmodulatorische Eigenschaften, die seine Fähigkeit widerspiegeln, die Transkription von Cytokin-Genen in aktivierten Lymphozyten zu blockieren. Cyclosporin hemmt ebenso eine Anzahl von allergischen Immunreaktionen, die nach Aktivierung von Mastzellen, Langerhans Zellen, Eosinophilen und Keratinozyten auftreten. In randomisierten, kontrollierten Untersuchungen hat sich Cyclosporin in einer Einleitungsdosierung von 5mg/kg zur Behandlung der caninen Atopie als genauso wirkungsvoll erwiesen wie Glukokortikoide. Der Wirkstoff hat auch zur Behandlung von Perianalfisteln als nützlich erwiesen. Andere potentielle Anwendungsbereiche deuten sich aus einer kleinen offenen Pilotstudie mit Hunden mit verschiedenen immun-medierten dermatologischen Erkrankungen an. Die pharmakokinetischen Eigenschaften von Cyclosporin sind beim Menschen und Hund sehr ähnlich, die Sicherheitsspanne jedoch ist beim Hund viel breiter. Deshalb scheint die routinemäßige Überwachung des Cyclosporinspiegels im Blut nicht notwendig zu sein. Während beim Menschen Schäden und Bluthochdruck in der Niere sogar bei niedrigen Dosierungen häufig festgestellt werden, wird dies beim Hund nicht beobachtet. Nebenwirkungen bestehen hauptsächlich aus vorübergehendem Erbrechen und Durchfall während der ersten Behandlungstage. Andere Nebenwirkungen wie Hyperplasie des Zahnfleisches, warzenähnliche Hautveränderungen und Hypertrichose scheinen dosisabhängig zu sein und treten bei therapeutischen Dosen nur selten auf. Von einer erhöhten Empfänglichkeit für Infektionen wurde bei Hunden, die dieses Medikament erhalten haben, nicht berichtet.

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