Review

OPEN ACCESS

Ciclosporin 10 years on: indications and efficacy

Peter Forsythe, Sue Paterson

Ciclosporin is a lipophilic cyclic polypeptide with powerful immunosuppressive and immunomodulatory properties that has been used in veterinary medicine for two decades. It is a calcineurin inhibitor whose principal mode of action is to inhibit T cell activation. The drug is principally absorbed from the small intestine and is metabolised in the intestine and liver by the cytochrome P450 enzyme system. Ciclosporin is known to interact with a wide range of pharmacological agents. Numerous studies have demonstrated good efficacy for the management of canine atopic dermatitis and this has been a licensed indication since 2003. In addition to the treatment of atopic dermatitis, it has been used as an aid in the management of numerous other dermatological conditions in animals including perianal fistulation, sebaceous adenitis, pododermatitis, chronic otitis externa and pemphigus foliaceus. This article reviews the mode of action, pharmacokinetics, indications for use and efficacy of ciclosporin in veterinary dermatology.

CICLOSPORIN is a lipophilic cyclic polypeptide with powerful immunosuppressive and immunomodulatory properties that is isolated from the fungus *Beauveria nivea* (formerly *Tolypocladium inflatum* Gams). It was first used in human medicine to prevent rejection of transplanted organs and later for the treatment of atopic dermatitis (AD) and psoriasis. It has now been used in veterinary medicine for over two decades and this article marks the fact that ciclosporin has now been licensed for the treatment of canine AD for 10 years. Ciclosporin has also been shown to be effective in, and is licensed for, the treatment of feline allergic skin disease (Wisselink and Willemse 2009). In addition to the treatment of allergic disease in cats and dogs, it has proved to be useful for the treatment of many other dermatological conditions in animals and there are many reports in the literature to this effect.

Mechanisms of action

Ciclosporin is a calcineurin inhibitor whose principal mode of action is to inhibit T cell activation. Ciclosporin achieves its immunosuppressive activity by binding to the intracellular receptor protein cyclophilin-1. The resulting ciclosporin-cyclophilin complex inhibits calcineurin, which prevents the dephosphorylation and activation of the transcription factor, nuclear factor of activated T cells (NF-AT) (Guaguère and others 2004). NF-AT helps regulate the production of several important pro-inflammatory cytokines including interleukin (IL)-2, IL-4, interferon-γ and tumour necrosis factor-α (Taylor and others 2005). It is the specific inhibition of IL-2, which plays a critical role in the activation and proliferation of T cells, that is thought to account for ciclosporin's main mechanism of immunosuppression, although there is recent evidence that NF-AT also interacts with other transcriptional factors that regulate T helper cell differentiation, T cell tolerance and thymocyte development (Macian 2005). In addition to the effect on T cells, there is increasing evidence that the NF-AT signalling pathway is also involved in innate immunity and regulates the homeostasis of cells involved in innate immune mechanisms. Therefore, ciclosporin influences both innate and adaptive immune responses (Fric and others 2012) and there is an increasing list of other cells involved in inflammatory and immune responses that may be affected by ciclosporin including B cells, antigen presenting cells, keratinocytes, endothelial cells, mast cells, basophils and eosinophils. The principal effects are listed in Table 1. The overall effect of ciclosporin is a reduction in the number and activity of proinflammatory cells at sites of inflammation.

Table 1: Modes of action of ciclosporin

Cell type	Mode of action of ciclosporin	References
T cells	Inactivation of NF-AT and reduced IL-2 production which suppresses T cells and T cell cytokine production (IL-4, 5,6,8,13, GM-CSF, TNF-α and IFN-γ)	Bunikowski and others 2001 Ho and others 1996 Matsuda and Koyasu 2000
B cells	Inhibits growth and activation of B cells. Minimal inhibition of antibody production or humoral response to vaccines in dogs	Brazis and others 2006 Bruner 2006 Guaguère and others 2004 Takaori and others 1992
Antigen presenting cells (APCs)	Reduces both the number and activity of APCs, especially Langerhans cells	Bussmann 2009
Basophils	Reduces degranulation, histamine release and leukotriene synthesis	Cirillo and others 1990
Eosinophils	Reduces degranulation, cytokine secretion, chemotaxis and longevity	Marsella and Olivry 2001 Sihra and others 1997
Endothelial cells	Reduces adhesion molecule expression	Cockerill and others 1995
Keratinocytes	Anti-proliferative effect and reduced cytokine production	Baumer and Kietzmann 2007 Won and others 1994
Mast cells	Reduces numbers, histamine release and cytokine production (1L-3, 4, 5, 8, TNF)	Brazis and others 2006 Hatfield and Roehm 1992 Oran and others 1997

GM-CSF Granulocyte macrophage colony cell stimulating factor, IFN Interferon, IL Interleukin, NF-AT Nuclear factor of activated T cells, TNF Tumour necrosis factor

Veterinary Record (2014) 174 (supplement 2), 13-21 doi: 10.1136/vr.102484

Peter Forsythe, BVM&S, DVD, MRCVS,
The Dermatology Referral Service, 528 Paisley Road West, Glasgow G51 1RN, UK
Sue Paterson, MA, VetMB, DVD, MRCVS,
Rutland House Referral Hospital, Abbotsfield Road, St Helens, Merseyside WA9 4HU, UK

E-mail for correspondence: peter.forsythe@btconnect.com

Provenance: not commissioned; externally peer reviewed

Table 2: Evidence for efficacy of ciclosporin (CsA) in canine atopic dermatitis

Type of study	Control group (number of dogs)	Treatment group (number of dogs)	Efficacy – lesions	Efficacy – pruritus	Level of evidence	References
Open		CsA 5 mg/kg (14)	Median lesion reduction 60% (after 2 weeks)	Median pruritus reduction 100% (after 2 weeks) Owner perceived efficacy excellent in 9/14 dogs	C3	Fontaine and Olivry 2001
RCT-DB	Prednisolone 0.5 mg/kg (15)	CsA 5 mg/kg (15)	Significant improvement in CsA treated group P<0.0001 >50% improvement in 69% cases No difference between CsA and prednisolone treated groups	Significant improvement in CsA treated group P=0.0003 >50% improvement in 77% cases No difference between CsA and prednisolone treated groups	A3	Olivry and others 2002a
RCT-DB	Placebo (30) CsA 2.5 mg/kg sid (30)	CsA 5 mg/kg (31)	Significant improvement in CsA (5 mg/kg sid) treated group compared to both control groups P=0.002 ≥50% reduction in lesion scores 22/31 cases treated with CsA 5 mg/kg after 6 weeks	Significant improvement in treatment group compared to placebo P value not given ≥50% reduction in pruritus 15/31 cases treated with CsA 5 mg/kg after 6 weeks	A2	Olivry and others 2002b
RCT-SB	Methylprednisolone (MP) (0.5^{-1} mg/kg) (59)	CsA 5 mg/kg (117)	Improvement over baseline after 8 weeks CsA group (53%); MP group (45%) No difference between groups	Owner pruritus scores improvement over baseline after 8 weeks CsA (39%); MP (38%) No difference between groups	A1	Steffan and others 2003
RCT-NB		CsA 5 mg/kg for 4 weeks (30) then either decreasing dosage to 2.5 and 1.25 mg/kg sid (15) or increasing intervals (CsA 5 mg/kg given every second or fourth day) (15)	37% of dogs with ≥50% reduction in CADESI scores after 4 weeks No difference between groups after 12 weeks	50% dogs with ≥50% reduction in pruritus after 4 weeks (owner assessments) No difference between groups after 12 weeks	B3	Olivry and others 2003b
Open		CsA 5 mg/kg (41)	Significant improvement in 41/41 dogs P<0.001 after 6 weeks	Significant improvement in 36/41 dogs P=0.00 after 6 weeks	C2	Burton and others 2004
Open		CsA 5 mg/kg (15)	20% dogs showed ≥50% reduction in lesion scores after 4 weeks (investigators assessment)	Overall 27% reduction in pruritus over baseline scores after 4 weeks (owners assessment)	C3	Bensignor and Guaguère 2004 (from Steffan and others 2006)
MET	Placebo (164)	CsA (165)	50% CsA treated vs 12% placebo treated dogs achieved ≥50% reduction in lesions scores after 6 weeks	38% CsA treated vs 19% placebo treated dogs achieved a level of mild pruritus (<3/5 pruritus score) after six weeks	A1	Olivry 2004
	Glucocorticoids (74)	CsA (132)	44% CsA treated and 53% glucocorticoid-treated dogs achieved ≥50% reduction in lesion scores after 6 weeks	38% CsA treated and 49% glucocorticoid-treated dogs achieved ≥50% reduction in pruritus after 6 weeks		
CS		CsA 5 mg/kg for at least six months (51)		After at least 6 months 28/55 dogs still treated with CsA. 8/28 (15%) 2 to 3 days per week; 10 (20%) 4 to 5 days per week; 10 (20%) daily 12/55 treatment discontinued due to remission* 11/55 CsA discontinued due to poor response (6) and cost (5)	D1	Radowicz and Power 2005

Pharmacokinetics

Ciclosporin was first produced as a vegetable oil formulation (Sandimmune; Novartis). The drug is principally absorbed from the small intestine and the absorption of this early formulation was dependent on bile flow and other factors resulting in variable and poor bioavailability (Guaguère and others 2004). A microemulsified (ME) product was subsequently developed that improved oral bioavailability, that was not dependent on bile flow for absorption and had less variable absorption. This formulation is licensed for treatment of canine AD (Atopica; Novartis Animal Health) and is available in 10, 25, 50 and 100 mg soft gelatin capsules; the active product being identical to the human formulation (Neoral; Novartis Pharmaceuticals). Administration of the microemulsion formulation to healthy beagles with food decreased the bioavailability by 22 per cent and increased the individual variability of drug absorption(Steffan and others 2004b) and the datasheet recommendation is that ciclosporin should be administered at least two hours before or after feeding. However, another study found that administration of ciclosporin with food to dogs treated for AD did not influence the clinical response (Thelen and others 2006) and clinical experience has shown that efficacy seems unaffected by administration with food. As will be discussed in more detail, absorption is also limited by the effects of p-glycoprotein efflux pumps present in the small intestine enterocytes (Wu and others 1995) and by metabolism of the drug by cytochrome P450 3A (CYP3A) enzymes also within the intestines (Whalen and others 1999). The bioavailability after oral administration of the ME formulation is 35 per cent in the dog (Guaguère and others 2004). The drug is metabolised mainly in the liver and intestine by CYP3A enzymes (Whalen and others 1999). There are numerous pharmacologically inactive metabolites (Fahr and others 1990) that are eliminated via the biliary system. The high margin of safety and the relatively long half-life of the drug (nine hours) mean once daily dosing is sufficient in the dog (Guaguère and others 2004). In addition, ciclosporin has been shown to concentrate in the skin after oral administration (Steffan and others 2003), further supporting once daily dosing.

Clinical aspects of drug interactions

Ciclosporin is known to interact with a wide range of pharmacological agents. These interactions have been well researched in people but only limited information is available in dogs. The two main mechanisms of drug interaction involve the CYP3A enzyme system and/or competition with the ATP binding transport protein P-glycoprotein (P-gp) (Steffan 2004). Commonly used veterinary medicines and other pharmacologically active compounds that may interact with ciclosporin include azole antifungals, metoclopramide, cimetidine, erythromycin, clindamycin, phenobarbital, vitamin E, grapefruit juice and St John's wort.

Table 2: condt

Type of study	Control group (number of dogs)	Treatment group (number of dogs)	Efficacy – lesions	Efficacy – pruritus	Level of evidence	References
RCT-DB	Placebo (soybean oil) (134)	CsA 5 mg/kg (134)	Mean CADESI score CsA treated group after 4 weeks significantly lower than baseline and placebo group P<0.001 ≥50% reduction in CADESI 45% CsA and 7% placebo	Mean owner pruritus score CsA treated group after 4 weeks significantly lower than baseline and placebo group P<0.001 % dogs with severe pruritus scores decreased from 67% to 16% after 4 weeks	A1	Steffan and others 2005
Open		CsA 5 mg/kg (266)	>50% reduction in CADESI scores in 68% cases after 8 weeks	% dogs with severe pruritus scores decreased from 64% to 15% after 8 weeks	C1	Steffan and others 2005
MET	Placebo (160) Oral glucocortiosteriods (74) Antihistamines (23)	672 CsA treated (672): 5 mg/kg (642); 2.5 mg/kg (30) 799 dogs in total	Lesion scores improved from baseline by 53 to 84% after 6 weeks Meta-analysis confirmed highly significant effects of CsA over placebo but not over glucocorticoids	After 4 to 6 weeks treatment ≥50% reduction in pruritus over baseline in 35% to 67% of cases Owner assessment of success in 48 to 67% of pets	A1	Steffan and others 2006
RCT-NB		CsA 5 mg/kg administered with food (15) CsA 5 mg/kg 2 hours before or after feeding (10)	28% dogs had ≥50% reduction in CADESI scores after 4 weeks 20/25 dogs had >50% reduction in CADESI scores after 6 months No difference between two groups at any time point to 6 months	44% dogs had ≥50% reduction in pruritus after 4 weeks 17/25 dogs had >50% reduction in pruritus after 6 months (owner assessment) No difference between two groups	B3	Thelen and others 2006
RCT-DB	Virbagen Omega (VO) 10 injections of rFeIFN-ω (1 to 5 million units according to bodyweight) over 6 months and placebo CsA-like capsules (18)	CsA 5 mg/kg sid for 2 months and then twice weekly for 4 months + placebo injections of VO excipient (8)	Significant reduction in lesions over baseline in both groups p<0.0001 ≥50% reduction in CADESI in 87.5% CsA treated cases after 8 weeks	Significant reduction of pruritus in both groups over baseline after 8 weeks (PICAD scoring) P<0.0001 ≥50% reduction in pruritus (PICAD) in 87.5% CsA treated cases after 8 weeks	A4	Carlotti and others 2009
RCT-SB	Prednisolone 1 mg/kg sid for 7 days then 1 mg/kg eod for 35 days (7)	CsA 5 mg/kg sid (human generic form) (13)	11/13 CsA treated and 6/7 prednisolone treated dogs had a ≥50% reduction in CADESI score after 6 weeks No difference between groups after 6 weeks	10/13 CsA treated, and 6/7 prednisolone treated dogs had ≥50% reduction in pruritus scores (investigator assessment) after 6 weeks No difference between groups after 6 weeks	A4	Kovalik and others 2011
RCT-SB	Hydrocortisone aceponate 0.585% (HCA) applied topically once daily (25)	CsA 5 mg/kg (23)	Significant improvement in both groups P<0.0001 ≥50% reduction in CADESI-03 after 84 days in 86.7% CsA and 75% HCA groups No difference between groups	Significant improvement in both groups P<0.0001 ≥50% reduction in pruritus after 84 days in 57.1% CsA and 66.6% HCA groups No difference between groups	A2	Nuttall and others 2012
RCT-NB	CsA 5 mg/kg sid and prednisolone 1 mg/kg sid for 7 days then eod for 14 days (23)	CsA 5 mg/kg sid (25)	Mean reduction in CADESI-03 in CsA and CsA + prednisolone treated groups after 28 days was 56.52% and 57.9% respectively The difference between groups was not significant	Mean reduction in pruritus in CsA and CsA + prednisolone treated groups after 28 days was 42.4% and 65.1% respectively The difference between groups was not significant	B2	Dip and others 2013
RCT-DB	Placebo spray (15)	Nanocapsule CsA spray on formulation (17)	Lesion score significantly lower in treatment compared baseline after 21 and 45 days P<0.01 No significant improvement in placebo group after 21 and 45 days	64% of treatment group had a ≥50% reduction in pruritus compared to 11% in placebo group after 45 days	A3	Puigdemont and others 2013

Open Clinical trial with no control, RCT-DB Randomised control trial – double blind, RCT-SB RCT – single blind, RCT-NB RCT – not blind, MET Meta-analysis, CS Retrospective case series, sid Once a day, eod Every other day, CADESI Canine atopic dermatitis extent and severity index, PICAD Pruritus index for canine atopic dermatitis
Level of evidence: A Blinded randomised controlled trial; B Controlled trial with blinding and/or randomisation; C Open trial with no control; D Case series, case report, anecdotal report etc. 1 >50 dogs/group; 2 20 to 50 dogs/group; 3 10 to 19 dogs/group; 4 <10 dogs/group
Explanation of level of evidence: The studies listed are categorised according to levels of evidence. This is dependent on the type of study and the number of subjects. Thus, the strongest level of evidence for efficacy are blinded, randomised controlled trials involving greater than 50 dogs per treatment group (A1). Conversely, the weakest evidence for efficacy is provided by case series or case reports involving less than 10 dogs (D4)

The technical aspects of these drug interactions are discussed in the article on pp 3-11 of this supplement (Nuttall and others 2014), so this section will be limited to discussion of the effect on clinical applications.

The azole antifungals inhibit CYP3A and therefore have the potential to reduce the dosage of ciclosporin required to achieve therapeutic concentrations. Ketoconazole, itraconazole and fluconazole have been shown to produce these dose sparing effects in both people and dogs. One study in healthy beagles showed that ketoconazole at dosages of 13.6 mg/kg once a day (sid) and 4.7 mg/kg sid allowed dosage reductions of ciclosporin of 75 per cent and 38 per cent respectively to still achieve similar blood concentrations (Dahlinger and others 1998). Fluconazole has a similar effect (Katayama and others 2008). These drug interactions have been used to decrease the cost of ciclosporin therapy, and a recent study concluded that administration of ciclosporin and ketoconazole concurrently at 2.5 mg/kg each may be as effective as ciclosporin alone at 5.0 mg/kg for treatment of canine AD (Gray and others 2013).

Clinicians should be aware that macrolide antibiotics such as erythromycin are highly metabolised by the hepatic CYP system and therefore have the potential to increase ciclosporin bioavailability. In people, erythromycin has been shown to increase bioavailability of ciclosporin from 75 per cent to 215 per cent (Campana and others 1996). A similar effect has been demonstrated in the dog with clarithromycin and erythromycin, whereas clindamycin and lincomycin did not increase ciclosporin availability (Steffan 2004, Katayama and others 2013). The interaction between ciclosporin and cimetidine, an H2 receptor antagonist and a potent inhibitor of the CYP 3A system, has been studied in dogs (Daigle and others 2001). This work demonstrated that cimetidine delayed but did not decrease the rate of absorption of ciclosporin. Metaclopramide has been shown to have no effect on the pharmacokinetic parameters of ciclosporin in healthy dogs (Radwanski and others 2011).

Two other chemicals that have been shown to affect ciclosporin blood levels are St John's wort and grapefruit juice. St John's wort is a herb that can affect the pharmacokinetics of many different

Table 3: Evidence of efficacy of ciclosporin (CsA) in perianal fistulation

Type of study	Treatment and control groups (number of dogs)	Efficacy – lesions	Level of evidence*	References
RCT-DB	CsA 5 mg/kg bid for 16 weeks (10) Placebo for 4 weeks then CsA 5 mg/kg bid for 12 weeks (10)	10/10 CsA dogs subjectively improved after 4 weeks Lesions healed in 17/20 dogs after 16 weeks 9/17 remained lesion free after 15 to 19 months following treatment withdrawal 8/17 lesions recurred within 24 weeks No placebo treated dogs improved	A3	Mathews and Sukhiani 1997
CS	CsA 7.5 mg/kg bid with food (6)	Reduction in lesion size of 50 to 90% in all cases after one week of treatment. Complete resolution in 5/6 cases in 10 to 20 weeks 5/6 cases remained lesion free 4 to 14 months after discontinuation of therapy One case relapsed 8 weeks after discontinuation of therapy	D4	Griffiths and others 1999
Open	CsA 1 mg/kg and ketoconazole 10 mg/kg sid (16)	13/16 dogs had complete resolution of lesions after 16 weeks 7/16 remained in remission for >12 months Recurrence seen in three dogs at 8, 10 and 12 months after treatment, and in three dogs within 1 month of treatment	C3	Mouatt 2002
Open	CsA 2.5 mg/kg bid (8) CsA 4 mg/kg sid (4) All 12 also ketoconazole 8 mg/kg sid	Remission of lesions in 8/12 dogs in 4 to 49 weeks (mean 13.9 weeks) Improvement in 3/12 dogs Recurrence of lesions in 5/8 cases that achieved remission in 5 to 22 weeks	C3	Patricelli and others 2002
Open	CsA 1.5 mg/kg (6) CsA 3 mg/kg (6) CsA 5 mg/kg (6) CsA 7.5 mg/kg (6) All groups treated for 13 weeks	Lesions improved, controlled or in remission in 17/24 cases. 7/24 cases failed to respond Lesions were controlled or in remission in 5/6, 4/6, 4/6 and 2/6 in 7.5, 5, 3 and 1.5 g/kg treated groups respectively 3/6 dogs in remission after 13 weeks relapsed in 2 to 6 months after discontinuation of therapy Response of the 7.5 mg/kg group was significantly better than the other three groups	C4	Doust and others 2003
Open	CsA 0.5, 0.75, 1 or 2 mg/kg bid, ketoconazole 5.3 to 8.9 mg/kg bid (19)	Complete resolution of lesions in 19/19 dogs in 3 to 10 weeks In 18/19 cases lesions resolved in ≤6 weeks 12/19 remained in remission (follow up 1 to 19 months) 7/19 had one or more recurrences 3 weeks to 6 months after discontinuation of therapy	C3	O'Neill and others 2004
Open	CsA 4 mg/kg bid until 2 weeks past lesion resolution or until no further improvement after 4 weeks (26)	25/26 improved Follow up was 1 to 20 months (mean 6.8 months) 18/26 had complete resolution. Of these, 6 recurred 7/26 improved but underwent surgery resection of residual lesions. Of these, 3 recurred Recurrence of lesions in 1 to 32 weeks (mean 10.4 weeks)	C2	Hardie and others 2005
CS	CsA 2.5 to 5 mg/kg bid (7) CsA 1 to 1.5 mg/kg bid combined with ketoconazole 12.5 mg/kg sid (11) Azathioprine 1 to 2 mg/kg sid combined with prednisolone 1 mg/kg bid for 2 weeks then 0.5 mg/kg bid (7) All dogs treated for up to 12 weeks then underwent surgical ablation of remaining lesions	Clinical signs resolved or greatly improved in all dogs although pinpoint draining tracts persisted in up to 10 CsA treated dogs and 5 azathioprine treated at surgery	D4	Klein and others 2006
RCT-SB	CsA 2 mg/kg sid (10) CsA 5 mg/kg sid (10)	2/10 in 2 mg/kg group and 6/10 in 5 mg/kg sid had complete resolution of lesions after 8 weeks Significantly faster lesion resolution with 5 mg/kg vs 2 mg/kg Long term follow up not given	A3	House and others 2006

* See footnote to Table 2
RCT-DB Randomised control trial – double blind, CS Retrospective case series, RCT-SB RCT – single blind, bid Twice a day, sid Once a day

drugs through induction of cytochrome P450 (CYP 2C and CYP 3A). It is this mechanism which is thought to decrease ciclosporin levels in people (Bauer and others 2003). A similar effect was demonstrated when St John's wort was given orally at a dose of 300 mg with ciclosporin at a dose of 5 mg/kg daily to dogs (Fukunaga and Orito 2012). Grapefruit juice contains furanocoumarins, which inhibit intestinal CYP 3A enzymes. This mechanism is thought to be responsible for the increase in bioavailability of ciclosporin in both people (Ku and others 1998) and dogs (Radwanski and others 2011) when grapefruit juice and ciclosporin are administered together.

A single dose of freeze-dried or liquid grapefruit juice significantly increased the bioavailability of orally administered ciclosporin in dogs (Amatori and others 2004). Radwanski (2011) used powdered whole grapefruit juice, which is expensive but has the potential to reduce the required orally administered dose of ciclosporin, although the amount required (at least 10 g) means this is currently not cost-effective (Radwanski and others 2011).

Phenobarbital is known to induce CYP enzymes leading to an increased elimination of ciclosporin. As a result of this phenobarbital has been shown to produce a significant reduction of up to 40 per cent in ciclosporin blood levels (Steffan 2004).

Indications for ciclosporin

Canine atopic dermatitis

Numerous studies have been published over the past 13 years that have demonstrated the safety and efficacy of ciclosporin in the management of canine AD (Table 2). Clinical experience has further supported the value of this drug. Published studies vary from case series to open, unblinded and uncontrolled studies, to high-quality, double-blinded randomised controlled trials (RCTs). The studies listed in Table 2 comprise some 727 dogs treated with ciclosporin. Overall results from the trials show that around one- to two-thirds of dogs will show a 50 per cent or more reduction in pruritus and lesion scores within four to eight weeks. A recent systematic review of RCTs for treatments of canine AD concluded that there were now multiple, high-quality RCTs that show the efficacy of oral ME ciclosporin given at a starting dose of 5 mg/kg for the management of canine AD (Olivry and Bizikova 2013). There was no difference demonstrated in efficacy between oral ciclosporin and prednisolone and oral ciclosporin and methylprednisolone for the management of canine AD with both lesional scores and pruritus responding to treatment (Olivry and others 2002a, Steffan and others 2004a, Kovalik and others 2011).

Ciclosporin is a relatively large molecule with poor dermal penetration but very recently, a nanocapsule ciclosporin spray-on formu-

Table 4: Ciclosporin (CsA) treatment of sebaceous adenitis

Type of study	Treatment and control groups (number of dogs)	Efficacy – lesions	Level of evidence*	References
CR	CsA 5 mg/kg bid (1)	Good clinical response for 12 months	D4	Carothers and others 1991
Open	CsA 2.3 mg/kg bid for 12 months (12)	Significant improvement in clinical scores after 4 months maintained for further 8 months Increase in the number of hair follicles with sebaceous glands after 12 months (2% to 40%)	C3	Linek and others 2005
RCT-DB	CsA 5 mg/kg (12) CSA 5 mg/kg + topical therapy (shampoos + propylene glycol) (12) Placebo capsules + topical therapy (shampoos + propylene glycol) (10)	Improvement in scaling: 29% in CsA alone vs 48% in the placebo/topical group vs 70% in the CsA/topical group Alopecia scores decreased in all three groups by 57-81% but no difference between groups Sebaceous gland scores significantly improved in all groups CsA group and the CsA/topical group showed higher levels of sebaceous glands than the placebo/topical therapy group	A3	Lortz and others 2010

* See footnote to Table 2
CR Case report, RCT-DB Randomised control trial – double blind, bid Twice a day

lation has been developed to enhance penetration with the view to topical therapy. The use of this product in a six-week RCT of 32 dogs showed an 87.5 per cent reduction in pruritus in the treatment group compared to 28.6 per cent in the placebo group. The authors concluded that this was a safe and effective therapy for the control of pruritus in canine AD (Puigdemont and others 2013), but this is a relatively small number of cases and larger scale trials are required.

Dosage and dosage reduction in canine atopic dermatitis

The recommended induction dosage rate of ciclosporin for the treatment of canine AD is 5 mg/kg every 24 hours. In many cases, once maximal response has been achieved generally after four weeks of treatment, it is possible to reduce the amount of drug administered without reducing efficacy. This may be by either reducing the daily dosage or increasing the interval between doses and there seems to be no difference between these two methods (Olivry and others 2003b). In one retrospective study of 51 dogs with AD treated long term with ciclosporin (Radowicz and Power 2005), 36 per cent required daily treatment, 36 per cent required treatment for four or five days per week and 28 per cent required treatment for two or three days per week. In this study, dosage reductions were decreased by drug withdrawal on one day per week if there was beneficial response. Dosage was not changed more frequently than once every four weeks. The rationale behind this is that some dogs may be maintained on a dosage somewhere between daily and alternate day therapy and one of the authors (PF) uses this approach. Another RCT reported that ultimately 50 per cent of cases required every other day therapy, 25 per cent twice weekly and 25 per cent daily therapy (Steffan and others 2003).

Reduction in the dosage is based on the clinical response to therapy rather than the measurement of serum levels of ciclosporin. In people serum ciclosporin levels are measured routinely in organ transplantation cases. In dogs the methodology is available to undertake routine monitoring and can be performed by a variety of different techniques. Those most commonly used include high-pressure liquid chromatography, fluorescent polarisation immunoassay and radioimmunoassay (Guaguère and others 2004). However, the interpretation of serum levels of ciclosporin in cases of canine AD is difficult because of the lack of clinical data correlating concentrations with response to therapy. Nevertheless, because the dosages of ciclosporin required in canine AD are much lower than the anti-rejection levels used in humans and because the safety margin is much greater in dogs, routine monitoring does not seem to be justified in general practice (Steffan and others 2004b). Blood levels measurement may, however, be useful when animals have failed to respond to appropriate levels of medication or if there is concern about toxicity when ciclosporin has been given over a prolonged period with another drug that is known to enhance bioavailability.

A blinded, prednisolone RCT (Olivry and others 2002a) looking at the reduction of pruritus produced by ciclosporin, at a dose of 5 mg/kg orally once daily, compared to prednisolone, at a dose of 0.5 mg/kg orally once daily, showed no significant difference in the reduction in pruritus in both groups. This suggested that the excellent reduction in pruritus score achieved within three weeks of starting ciclosporin therapy should make it a valuable alternative to glucocorticoid therapy in dogs with AD. However, as many dogs with AD exhibit severe pruritus accompanying self-inflicted trauma, more recent work has focussed on combinations of drugs, especially using glucocorticoids with ciclosporin, to try and improve its speed of action. Concurrent administration of ciclosporin with methylprednisolone has been shown in people to have variable effects. Some studies have shown a decrease in blood concentrations of ciclosporin, others have shown no change (Campana and others 1996). In dogs methylprednisolone was given at a dose of 1 mg/kg daily with ciclosporin at a high dose rate of 20 mg/kg daily without resulting in any interaction or adverse effects (Guaguère and others 2004). Concurrent administration of prednisolone with ciclosporin has been investigated as a means of accelerating the reduction in pruritus (Dip and others 2013). In a comparison of therapeutic response in two groups of atopic dogs given either ciclosporin alone at a dose of 5 mg/kg orally once daily or with prednisolone at a dose of 1 mg/kg orally once daily for 14 days then on an alternate day basis both owners and investigators agreed that concurrent therapy with prednisolone resulted in a quicker improvement in the dogs' overall skin condition and reduction in pruritus.

Longer term remission of clinical signs of dogs with non-seasonal AD has been recorded in animals treated with both glucocorticoids and ciclosporin. In a comparative study using methylprednisolone and ciclosporin (Steffan and others 2004a), workers demonstrated that although 87 per cent of dogs treated with methylprednisolone relapsed within two months of cessation of therapy only 62 per cent of dogs treated with ciclosporin showed a similar deterioration. Similarly, in a retrospective study of long-term management of canine AD with ciclosporin (Radowicz and Power 2005), in 12 out of 51 cases (24 per cent) it was possible to reduce and ultimately withdraw ciclosporin therapy without recurrence of clinical signs. These dogs remained in remission for a mean duration of 12 months following treatment withdrawal.

Use with allergen-specific immunotherapy

Allergen-specific immunotherapy (ASIT) offers an alternative to either glucocorticoids or ciclosporin therapy where either the cost or side effects of medication are a problem. Identification of putative allergens is required for the formulation of ASIT and ciclosporin has been shown to have no statistically significant effects on either intradermal or serum IgE allergy tests when administered at therapeutic dose rates of 5 mg/kg orally once daily for 30 days (Goldman and others 2010). It has therefore proved to be a useful drug to use for short-term control of AD to facilitate glucocorticoid withdrawal, allergy testing and the institution of ASIT. No work has been undertaken on the effect of ciclosporin on ASIT. However, many veterinary dermatologists routinely use ciclosporin during the induction and maintenance phase of ASIT

Table 5: Evidence for efficacy of ciclosporin (CsA) in miscellaneous skin diseases

Disease	Type of study (number of dogs)	Treatment	Efficacy – lesions	Level of evidence*	References
Canine cutaneous and systemic histiocytosis	CS (44)	3 dogs with systemic histiocytosis treated with CsA. Dosage not given	Good therapeutic success in 3/3 dogs treated with CsA	D4	Affolter and Moore 2000
Cutaneous reactive histiocytosis	CS	1 dog treated with ketoconazole 10 mg/kg sid and CsA 4 mg/kg sid in one dog, dosage not given for other dog	Complete resolution of lesions in 67 days for one dog; not given for the other dog Both dogs maintained on combination of ketoconazole/CsA	D4	Palmeiro and others 2007
Juvenile cellulitis	CR (1)	Refractory to topical and systemic dexamethasone Started CsA 5 mg/kg sid along with dexamethasone 0.02 mg/kg eod for two weeks then every 72 hrs	Marked improvement after 4 weeks. Lymphadenopathy persisted and CsA increased to 10 mg/kg sid Dexamethasone reduced to once weekly then withdrawn after 4 weeks when complete resolution of all signs CsA tapered and withdrawn after further 3-4 months Dog remained in remission	D4	Santoro and Campbell 2011
Sterile nodular panniculitis and vasculitis	CR (1)	Prednisolone 0.5 mg/kg sid CsA 5 mg/kg sid	Excellent response after 20 weeks	D4	Dandrieux and others 2011
Sterile nodular panniculitis	CS (2)	CsA 5 mg/kg	80% improvement after 2 weeks Complete resolution after 6 weeks	D4	Guaguère 2000
	CS (10)	Various immunosuppressive therapies 2 dogs treated with oral prednisolone 1 mg/kg bid and CsA 5 mg/kg sid	Resolution of clinical lesions within one week	D4	Kim and others 2011
Focal metatarsal sinus tracts	CR (1)	CsA 5 mg/kg for 2 months	Complete resolution after 2 months Recurrence when dosage reduced to 5 mg/kg eod then further resolution when increased to daily therapy	D4	Oliveira and others 2007
Pemphigus foliaceus	CS (5)	CsA 5 to 10 mg/kg sid for 1 to 3 months	Lesion scores worsened in 4/5 dogs CsA was ineffective as a sole agent when used at these doses to treat canine pemphigus foliaceus	D4	Olivry and others 2003
	CS (5)	Prednisolone 1 to 2.6 mg/kg sid tapered over 20 to 36 weeks to 0.5 mg/kg sid CsA 5 to 18 mg/kg sid for 8 to 39 months then tapered to 3 to 4 mg/kg sid after resolution of lesions CsA administered as maintenance for 1 to 18 months	Complete resolution in 4/5 and partial in 1/5 Lesions recurred in 3/5 cases after cessation of CsA maintenance therapy Further resolution when CsA restarted CsA reduced prednisolone dosage required	D4	Maeda and others 2008
	CS (3)	Three cases previously treated with azathioprine (AZA) and glucocorticoids without response Induction therapy: ketoconazole 2.5 to 5 mg/kg sid; CsA 7.5 to 8 mg/kg sid; AZA 1.5 to 2.5 mg/kg sid plus glucocorticoids Dosages tapered to CsA 2.5 to 5 mg/kg eod, AZA 1.5 to 2.5 mg/kg eod; ketoconazole 2.5 to 5 mg/kg eod	All cases in remission after 10 to 18 months It was possible to withdraw glucocorticoids 3 to 12 weeks after addition of CsA	D4	Rosenkrantz and Aniya 2007
Vesicular cutaneous lupus erythematosus	CR (1)	CsA 4 mg/kg sid Ketoconazole 4 mg/kg sid Prednisolone 0.2 mg/kg bid (for 22 days)	Resolution of lesions after 2.5 months	D4	Font and others 2006
Exfoliative cutaneous lupus erythematosus	CS (6)	Four dogs treated with CsA 5 to 10 mg/kg sid	Improvement in lameness and erythema in 1 to 2 weeks but did not slow overall progression of disease	D4	Mauldin and others 2010
Alopecia areata	CR (1)	CsA 5 mg/kg sid for one month then 5 mg/kg eod for 2 months	Complete remission of clinical lesions	D4	Noli and Toma 2006
Uveodermatologic syndrome	CR (1)	CsA 4.7 mg/kg sid Prednisolone 0.6 mg/kg sid then eod	Skin lesions controlled over 10 month period	D4	Blackwood and others 2011
Pyoderma gangrenosum	CR (1)	CsA 5 mg/kg sid Prednisolone 1 mg/kg bid for 7 days, 1 mg/kg sid for 7 days then 1 mg/kg eod 28 days then 0.5 mg/kg eod	Complete resolution after 8 weeks	D4	Bardagi and others 2007
Proliferative infundibular mural folliculitis and dermatitis (labrador retrievers)	CS (4)	CsA 5 to 6.2 mg/kg sid in 3 dogs Prednisone 0.65 to 2 mg/kg sid; AZA (1.6 mg/kg sid); CsA 3.2 mg/kg sid	Rapid response to ciclosporin in all cases Two dogs remained in remission for at least 7 and 8 months after discontinuation of therapy	D4	Hargis and others 2013
Idiopathic chronic pododermatitis	Open (13) (7)	Prednisolone 2 mg/kg sid CsA 5 mg/kg sid	Marked clinical improvement over 2 to 8 weeks	C4	Breathnach and others 2005
End stage proliferative otitis externa	CS (5)	CsA 5 mg/kg bid for at least 12 weeks	Significant clinical improvement and improved quality of life	D4	Hall and others 2003

* See footnote to Table 2
CS Retrospective case series, CR Case report, Open Clinical trial with no control, bid Twice a day, sid Once a day, eod Every other day, bid Twice a day

without any apparent reduction in efficacy. Successful ASIT in dogs has been shown to be linked to an increase in the T regulatory cell population (Keppel and others 2008). In atopic humans, low dose ciclosporin therapy has been shown to significantly increase the T regulatory cell populations (Brandt and others 2009) suggesting that ciclosporin therapy may be synergistic with ASIT. Obviously this link needs further investigation.

Canine perianal fistulae

Canine perianal fistulae (PAF) is a chronic, progressive disease characterised by the development of cutaneous and retrocutaneous fistulae with associated ulceration around the perianal tissues. The condition is mainly confined to German shepherd dogs but can affect other breeds as well. Clinical signs include perineal pain, dyschezia, tenesmus, constipation and perineal discharge. The condition is

painful and debilitating. An immune-mediated cause is suspected (Kennedy and others 2008) and for this reason ciclosporin has been used to treat this disease. A literature search revealed eight studies describing the use of ciclosporin to treat PAF (Table 3). Two of these studies were RCTs and the remainder were open trials or case series. Drug doses, outcome measures and follow up vary considerably between studies. Drug doses in particular vary from 1.5 mg/kg sid to 7.5 mg/kg twice a day (bid) and so comparison between studies and pooling of data is not possible. Several studies used a combination of ciclosporin with ketoconazole to reduce cost. Overall, ciclosporin has been shown to be effective for the management of PAF and one RCT showed resolution of lesions in six of 10 cases treated with ciclosporin at a dosage of 5 mg/kg sid (House and others 2006). Higher dosages seem to result in more rapid resolution of signs (Griffiths and others 1999). Follow-up periods vary but some cases do appear to go into long-term remission. Even in those cases where signs recur, repeat treatment is often successful (Patricelli and others 2002). In conclusion, ciclosporin appears to be effective for the management of PAF but further controlled studies on the use of ciclosporin to treat PAF are required to elucidate the optimum dosage and duration of therapy.

Sebaceous adenitis

Sebaceous adenitis is an uncommon, scaling skin disease with variable alopecia and pruritus and is characterised by follicular cast formation. The standard poodle, English springer spaniel, Japanese akita, samoyed and Hungarian viszla are predisposed. Histologically, there is progressive destruction of sebaceous glands and an associated nodular granulomatous to pyogranulomatous inflammation consisting of histiocytes, lymphocytes and neutrophils. The pathogenesis is unknown but lipid abnormalities, a structural glandular or ductal defect and autoimmunity (Rybnicek and others 1998) have all been postulated as possible causes. Ciclosporin has been used to treat sebaceous adenitis because of its immunomodulatory properties and also because it initiates anagen and thus stimulates hair growth. In an uncontrolled open trial (Linek and others 2005) (Table 4), 12 dogs were treated with ciclosporin at a dosage of 2.3 mg/kg bid. After four months there was a significant improvement in clinical scores and subjectively, both the extent of alopecia and the severity of scaling improved in all dogs, resulting in a markedly improved hair coat quality. However, sebaceous adenitis is usually treated with topical therapy including keratolytic shampoos and moisturisers such as propylene glycol, and a controlled study compared the use of ciclosporin alone, ciclosporin with topical therapy, and topical therapy alone for the management of sebaceous adenitis (Lortz and others 2010). There was no difference between the groups with respect to improvement in alopecia scores but there was a marked reduction in scaling with the use of topical therapy in addition to ciclosporin and the group treated with a placebo and topical therapy responded better than the group treated with ciclosporin alone, underlining the importance of topical therapy for sebaceous adenitis.

Other indications

In addition to its use in canine AD, perianal fistulation and sebaceous adenitis, ciclosporin has also been used for many other presumed immune-mediated and autoimmune diseases (Table 5). Most of these are single case reports of relatively uncommon to rare diseases so the level of evidence for efficacy is low. Nevertheless, the majority of these reports are of a successful outcome and are the best evidence available at the present time. It is worth pointing out however, that ciclosporin is reported to be ineffective for the treatment of epitheliotrophic cutaneous lymphoma (Rosenkrantz and others 1989).

Chronic pododermatitis

Chronic pododermatitis is a common presentation in many breeds. In most cases a specific underlying cause can be identified such as demodicosis, deep pyoderma, poor confirmation or AD. However, in some cases, despite a thorough work up, a specific cause remains elusive. One study reported success in using ciclosporin to treat idiopathic pododermatitis in seven dogs (Breathnach and others 2005).

Chronic proliferative otitis externa

Chronic proliferative otitis externa (CPOE) is also a common clinical presentation, particularly in the cocker spaniel (Angus and others 2002). Underlying primary causes of inflammation may be identified, but addressing these is unlikely to resolve the proliferative disease and most cases require total ear canal ablation. One small pilot study found that ciclosporin was useful in the management of CPOE and while lesions and infection persisted, the dogs' quality of life greatly improved with therapy and this is worth considering where surgical therapy is not an option for whatever reason.

Pemphigus foliaceus

Pemphigus foliaceus is a pustular and crusting autoimmune disease, usually treated using systemic immunosuppressive therapy with glucocorticoids with or without additional immunosuppressive agents (Rosenkrantz 2004). In one small pilot study, ciclosporin as a sole agent was ineffective in controlling skin lesions (Olivry and others 2003a), but in another study lesion remission was induced in all cases when ciclosporin was administered along with prednisolone. It was possible to reduce maintenance dosage of prednisolone to 0.5 mg/kg every other day suggesting a possible glucocorticoid sparing effect of ciclosporin (Maeda and others 2008). Furthermore, it was possible to withdraw glucocorticoid therapy and maintain remission in three refractory cases of canine pemphigus foliaceus that had not responded to a combination of azathioprine and prednisolone following the addition of ciclosporin (Rosenkrantz and Aniya 2007).

Summary

Over the past 10 years, ciclosporin, a calcineurin inhibitor, has proven to be a very safe and effective therapy for the management of a variety of dermatological conditions in dogs. In particular, its use in the treatment of canine AD is well documented. Its relatively slow onset of action can be ameliorated by the additional use of glucocorticoid therapy for the first two to three weeks of therapy. Once maximal therapeutic effect has been achieved, a very slow reduction in dosage is advisable to identify those cases that can be managed on treatment levels somewhere between daily and alternate day, or alternate day and twice weekly administration.

There is also variable evidence that ciclosporin is useful in the management of many other immune-mediated skin diseases.

Conflict of interests

Peter Forsythe has received consultancy and lecture fees from Novartis Animal Health.

References

AFFOLTER, V. K. & MOORE, P. F. (2000) Canine cutaneous and systemic histiocytosis: reactive histiocytosis of dermal dendritic cells. *American Journal of Dermatopathology* **22,** 40-48

AMATORI, F. M., GIUSIANI, V. M. M., SOLDANI, G., CORAZZA, M. & GIORGI, M. (2004) Effect of grapefruit juice on the pharmacokinetics of cyclosporine in dogs. *Veterinary Record* **154,** 180-181

ANGUS, J. C., LICHTENSTEIGER, C., CAMPBELL, K. L. & SCHAEFFER, D. J. (2002) Breed variations in histopathologic features of chronic severe otitis externa in dogs: 80 cases (1995-2001). *Journal of the American Veterinary Medical Association* **221,** 1000-1006

BARDAGI, M., LLORET, A., FONDATI, A. & FERRER, L. (2007) Neutrophilic dermatosis resembling pyoderma gangrenosum in a dog with polyarthritis. *Journal of Small Animal Practice* **48,** 229-232

BAUER, S., STORMER, E., JOHNE, A., KRUGER, H., BUDDE, K., NEUMAYER, H. H., ROOTS, I. & MAI, I. (2003) Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *British Journal of Clinical Pharmacology* **55,** 203-211

BAUMER, W. & KIETZMANN, M. (2007) Effects of cyclosporin A and cilomilast on activated canine, murine and human keratinocytes. *Veterinary Dermatology* **18,** 107-114

BENSIGNOR, E. & GUAGUÈRE, E. (2004) Utilisation de la ciclosporine pour le traitement des formes rebelles de dermatite atopique canine. *Pratique Medicale et Chirurgicale de l'Animal de Compagnie* **39,** 15-19

BLACKWOOD, S. E., BARRIE, K. P., PLUMMER, C. E., TAYLOR, D., NUNNERY, C. M., SELTZER, J. D., BEN-SHLOMO, G. & BROOKS, D. E. (2011) Uveodermatologic syndrome in a rat terrier. *Journal of the American Animal Hospital Association* **47,** e56-63

BRANDT, C., PAVLOVIC, V., RADBRUCH, A., WORM, M. & BAUMGRASS, R. (2009) Low-dose cyclosporine A therapy increases the regulatory T cell population in patients with atopic dermatitis. *Allergy* **64,** 1588-1596

BRAZIS, P., BARANDICA, L., GARCIA, E., CLOUGH, G. F., CHURCH, M. K. & PUIGDEMONT, A. (2006) Dermal microdialysis in the dog: in vivo assessment of the effect of cyclosporin A on cutaneous histamine and prostaglandin D2 release. *Veterinary Dermatology* **17,** 169-174

BREATHNACH, R. M., BAKER, K. P., QUINN, P. J., MCGEADY, T. A., AHERNE, C. M. & JONES, B. R. (2005) Clinical, immunological and histopathological findings in a subpopulation of dogs with pododermatitis. *Veterinary Dermatology* **16,** 364-372

BRUNER, S. R. (2006) Updates in therapeutics for veterinary dermatology. *Veterinary Clinics of North America: Small Animal Practice* **36,** 39-58, vi

BUNIKOWSKI, R., GERHOLD, K., BRAUTIGAM, M., HAMELMANN, E., RENZ, H. & WAHN, U. (2001) Effect of low-dose cyclosporin a microemulsion on disease severity, interleukin-6, interleukin-8 and tumor necrosis factor alpha production in severe pediatric atopic dermatitis. *International Archive of Allergy and Immunology* **125,** 344-348

BURTON, G., BURROWS, A., WALKER, R., ROBSON, D., BASSETT, R., BRYDEN, S. & HILL, A. (2004) Efficacy of cyclosporin in the treatment of atopic dermatitis in dogs--combined results from two veterinary dermatology referral centres. *Australian Veterinary Journal* **82,** 681-685

BUSSMANN, C., BIEBER, T. & NOVAK, N. (2009) Systemic therapeutic options for severe atopic dermatitis. *Journal of the German Society of Dermatology* **7,** 205-219

CAMPANA, C., REGAZZI, M., BUGGIA, I. & MOLINARO, M. (1996) Clinically significant drug interactions with cyclosporin – an update. *Clinical Pharmacokinetics* **30,** 141-179

CARLOTTI, D. N., BOULET, M., DUCRET, J., MACHICOTE, G., JASMIN, P., REME, C. A. & ALBOUY, M. (2009) The use of recombinant omega interferon therapy in canine atopic dermatitis: a double-blind controlled study. *Veterinary Dermatology* **20,** 405-411

CAROTHERS, M. A., KWOCHKA, K. W. & ROJKO, J. L. (1991) Cyclosporine-responsive granulomatous sebaceous adenitis in a dog. *Journal of the American Veterinary Medical Association* **198,** 1645-1648

CIRILLO, R., TRIGGIANI, M., SIRI, L., CICCARELLI, A., PETTIT, G. R., CONDORELLI, M. & MARONE, G. (1990) Cyclosporin A rapidly inhibits mediator release from human basophils presumably by interacting with cyclophilin. *Journal of Immunology* **144,** 3891-3897

COCKERILL, G. W., BERT, A. G., RYAN, G. R., GAMBLE, J. R., VADAS, M. A. & COCKERILL, P. N. (1995) Regulation of granulocyte-macrophage colony-stimulating factor and E-selectin expression in endothelial cells by cyclosporin A and the T-cell transcription factor NFAT. *Blood* **86,** 2689-2698

DAHLINGER, J., GREGORY, C. & BEA, J. (1998) Effect of ketoconazole on cyclosporine dose in healthy dogs. *Veterinary Surgery* **27,** 64-68

DAIGLE, J. C., HOSGOOD, G., FOIL, C. S. & HUNTER, R. P. (2001) Effect of cimetidine on pharmacokinetics of orally administered cyclosporine in healthy dogs. *American Journal of Veterinary Research* **62,** 1046-1050

DANDRIEUX, J. R., TIMM, K., ROOSJE, P. J., WELLE, M., HOWARD, J., BRUHSCHWEIN, A. & FRANCEY, T. (2011) Unusual systemic signs in a dog with sterile neutrophilic-macrophagic lymphadenitis and nodular panniculitis. *Journal of the American Animal Hospital Association* **47,** 117-121

DIP, R., CARMICHAEL, J., LETELLIER, I., STREHLAU, G., ROBERTS, E., BENSIGNOR, E. & ROSENKRANTZ, W. (2013) Concurrent short-term use of prednisolone with cyclosporine A accelerates pruritus reduction and improvement in clinical scoring in dogs with atopic dermatitis. *BMC Veterinary Research* doi: 10.1186/1746-6148-9-173

DOUST, R., GRIFFITHS, L. G. & SULLIVAN, M. (2003) Evaluation of once daily treatment with cyclosporine for anal furunculosis in dogs. *Veterinary Record* **152,** 225-229

FAHR, A., HIESTAND, P. & RYFFEL, B. (1990) Studies on the biologic activities of Sandimmun metabolites in humans and in animal models: review and original experiments. *Transplantation Proceedings* **22,** 1116-1124

FONT, A., BARDAGI, M., MASCORT, J. & FONDEVILA, D. (2006) Treatment with oral cyclosporin A of a case of vesicular cutaneous lupus erythematosus in a rough collie. *Veterinary Dermatology* **17,** 440-442

FONTAINE, J. & OLIVRY, T. (2001) Treatment of canine atopic dermatitis with cyclosporine: a pilot clinical study. *Veterinary Record* **148,** 662-663

FRIC, J., ZELANTE, T., WONG, A. Y., MERTES, A., YU, H. B. & RICCIARDI-CASTAGNOLI, P. (2012) NFAT control of innate immunity. *Blood* **120,** 1380-1389

FUKUNAGA, K. & ORITO, K. (2012) Time-course effects of St John's wort on the pharmacokinetics of cyclosporine in dogs. *Journal of Veterinary Pharmacology and Therapeutics* **35,** 446-451

GOLDMAN, C., ROSSER, Jr, E., PETERSEN, A. & HAUPTMAN, J. (2010) Investigation on the effects of ciclosporin (Atopica) on intradermal test reactivity and allergen-specific immunoglobulin (IgE) serology in atopic dogs. *Veterinary Dermatology* **21,** 393-399

GRAY, L. L., HILLIER, A., COLE, L. K. & RAJALA-SCHULTZ, P. J. (2013) The effect of ketoconazole on whole blood and skin ciclosporin concentrations in dogs. *Veterinary Dermatology* **24,** 118-125

GRIFFITHS, L. G., SULLIVAN, M. & BORLAND, W. W. (1999) Cyclosporine as the sole treatment for anal furunculosis: preliminary results. *Journal of Small Animal Practice* **40,** 569-572

GUAGUÈRE, E. (2000) Efficacy of ciclosporin in the treatment of idiopathic sterile nodular panniculitis in two dogs. *Veterinary Dermatology* **11** (suppl 1), 22

GUAGUÈRE, E., STEFFAN, J. & OLIVRY, T. (2004) Cyclosporin A: a new drug in the field of canine dermatology. *Veterinary Dermatology* **15,** 61-74

HALL, J. A., WAISGLASS, S. E., MATHEWS, K. A. & TAIT, J. L. (2003) Oral cyclosporin in the treatment of end-stage ear disease: a pilot study. *Veterinary Dermatology* **14,** 212

HARDIE, R. J., GREGORY, S. P., TOMLIN, J., STURGEON, C., LIPSCOMB, V. & LADLOW, J. (2005) Cyclosporine treatment of anal furunculosis in 26 dogs. *Journal of Small Animal Practice* **46,** 3-9

HARGIS, A. M., MYERS, S., GORTEL, K., DUCLOS, D. & RANDOLPH-HABECKER, J. (2013) Proliferative, lymphocytic, infundibular mural folliculitis and dermatitis with prominent follicular apoptosis and parakeratotic casts in four Labrador retrievers: preliminary description and response to therapy. *Veterinary Dermatology* **24,** 346-354, e376-347

HATFIELD, S. M. & ROEHM, N. W. (1992) Cyclosporine and FK506 inhibition of murine mast cell cytokine production. *Journal of Pharmacology and Experimental Therapeutics* **260,** 680-688

HO, S., CLIPSTONE, N., TIMMERMANN, L., NORTHROP, J., GRAEF, I., FIORENTINO, D., NOURSE, J. & CRABTREE, G. R. (1996) The mechanism of action of cyclosporin A and FK506. *Clinical Immunology and Immunopathology* **80,** S40-45

HOUSE, A. K., GUITIAN, J., GREGORY, S. P. & HARDIE, R. J. (2006) Evaluation of the effect of two dose rates of cyclosporine on the severity of perianal fistulae lesions and associated clinical signs in dogs. *Veterinary Surgery* **35,** 543-549

KATAYAMA, M., IGARASHI, H., TANI, K., NEZU, Y., HARADA, Y., YOGO, T., HARA, Y., AOKI, S. & TAGAWA, M. (2008) Effect of multiple oral dosing of fluconazole on the pharmacokinetics of cyclosporine in healthy beagles. *Journal of Veterinary Medical Science* **70,** 85-88

KATAYAMA, M., KAWAKAMI, Y., KATAYAMA, R., SHIMAMURA, S., OKAMURA, Y. & UZUKA, Y. (2013) Preliminary study of effects of multiple oral dosing of clarithromycin on the pharmacokinetics of cyclosporine in dogs. *Journal of Veterinary Medical Science* Nov 5, epub

KENNEDY, L. J., O'NEILL, T., HOUSE, A., BARNES, A., KYOSTILA, K., INNES, J., FRETWELL, N., DAY, M. J., CATCHPOLE, B., LOHI, H. & OLLIER, W. E. (2008) Risk of anal furunculosis in German shepherd dogs is associated with the major histocompatibility complex. *Tissue Antigens* **71,** 51-56

KEPPEL, K. E., CAMPBELL, K. L., ZUCKERMANN, F. A., GREELEY, E. A., SCHAEFFER, D. J. & HUSMANN, R. J. (2008) Quantitation of canine regulatory T cell populations, serum interleukin-10 and allergen-specific IgE concentrations in healthy control dogs and canine atopic dermatitis patients receiving allergen-specific immunotherapy. *Veterinary Immunology and Immunopathology* **123,** 337-344

KIM, H. J., KANG, M. H., KIM, J. H., KIM, D. & PARK, H. M. (2011) Sterile panniculitis in dogs: new diagnostic findings and alternative treatments. *Veterinary Dermatology* 22, 352-359

KLEIN, A., DENEUCHE, A., FAYOLLE, P., HIDALGO, A., SCOTTI, S., ZYLBERSTEIN, L., DESBOIS, C., TESSIER, D., MOISSONNIER, P. & VIATEAU, V. (2006) Preoperative immunosuppressive therapy and surgery as a treatment for anal furunculosis. *Veterinary Surgery* **35,** 759-768

KOVALIK, M., TASZKUN, I., POMORSKI, Z., KOZAK, M., POMORSKA, D., SZCZEPANIK, M. & OTHERS (2011) Evaluation of a human generic formulation of ciclosporin in the treatment of canine atopic dermatitis with in vitro assessment of the functional capacity of phagocytic cells. *Veterinary Record* doi: 10.1136/vr.c7365

KU, Y. M., MIN, D. I. & FLANIGAN, M. (1998) Effect of grapefruit juice on the pharmacokinetics of microemulsion cyclosporine and its metabolite in healthy volunteers: does the formulation difference matter? *Journal of Clinical Pharmacology* **38,** 959-965

LINEK, M., BOSS, C., HAEMMERLING, R., HEWICKER-TRAUTWEIN, M. & MECKLENBURG, L. (2005) Effects of cyclosporine A on clinical and histologic abnormalities in dogs with sebaceous adenitis. *Journal of the American Veterinary Medical Association* **226,** 59-64

LORTZ, J., FAVROT, C., MECKLENBURG, L., NETT, C., RUFENACHT, S., SEEWALD, W. & LINEK, M. (2010) A multicentre placebo-controlled clinical trial on the efficacy of oral ciclosporin A in the treatment of canine idiopathic sebaceous adenitis in comparison with conventional topical treatment. *Veterinary Dermatology* **21,** 593-601

MACIAN, F. (2005) NFAT proteins: key regulators of T-cell development and function. *Nature Reviews Immunology* **5,** 472-484

MAEDA, H., TAKAHASHI, M., NAKASHIMA, K., FUJINO, Y., OHNO, K., TSUJIMOTO, H., TAKAHASHI, K., KANAMARU, A. & FUKAMACHI, T. (2008) Treatment of five dogs with pemphigus foliaceus with cyclosporine and prednisolone. *Veterinary Dermatology* **19,** 51

MARSELLA, R. & OLIVRY, T. (2001) The ACVD task force on canine atopic dermatitis (XXII): nonsteroidal anti-inflammatory pharmacotherapy. *Veterinary Immunology and Immunopathology* **81,** 331-345

MATHEWS, K. A. & SUKHIANI, H. R. (1997) Randomized controlled trial of cyclosporine for treatment of perianal fistulas in dogs. *Journal of the American Veterinary Medical Association* **211,** 1249-1253

MATSUDA, S. & KOYASU, S. (2000) Mechanisms of action of cyclosporine. *Immunopharmacology* **47,** 119-125

MAULDIN, E. A., MORRIS, D. O., BROWN, D. C. & CASAL, M. L. (2010) Exfoliative cutaneous lupus erythematosus in German shorthaired pointer dogs: disease development, progression and evaluation of three immunomodulatory drugs (ciclosporin, hydroxychloroquine, and adalimumab) in a controlled environment. *Veterinary Dermatology* **21,** 373-382

MOUATT, J. G. (2002) Cyclosporin and ketoconazole interaction for treatment of perianal fistulas in the dog. *Australian Veterinary Journal* **80,** 207-211

NOLI, C. & TOMA, S. (2006) Three cases of immune-mediated adnexal skin disease treated with cyclosporin. *Veterinary Dermatology* **17,** 85-92

NUTTALL, T. J., MCEWAN, N. A., BENSIGNOR, E., CORNEGLIANI, L., LOWENSTEIN, C. & REME, C. A. (2012) Comparable efficacy of a topical 0.0584%

hydrocortisone aceponate spray and oral ciclosporin in treating canine atopic dermatitis. *Veterinary Dermatology* **23,** 4-10, e11-12
NUTTALL, T., REECE, D. & ROBERTS, E. (2014) Life-long diseases need life-long treatment: long-term safety of ciclosporin in canine atopic dermatitis. *Veterinary Record* **174** (suppl 2), 3-11
O'NEILL, T., EDWARDS, G. A. & HOLLOWAY, S. (2004) Efficacy of combined cyclosporine A and ketoconazole treatment of anal furunculosis. *Journal of Small Animal Practice* **45,** 238-243
OLIVEIRA, A. M., OBWOLO, M. J., VAN DEN BROEK, A. H. & THODAY, K. L. (2007) Focal metatarsal sinus tracts in a Weimaraner successfully managed with ciclosporin. *Journal of Small Animal Practice* **48,** 161-164
OLIVRY, T. (2004) A systematic review and meta-analysis of the efficacy of cyclosporine for treatment of canine atopic dermatitis. 5th World Congress of Veterinary Dermatology. Proceedings of the Atopica Symposium. Vienna. pp 4-14
OLIVRY, T. & BIZIKOVA, P. (2013) A systematic review of randomized controlled trials for prevention or treatment of atopic dermatitis in dogs: 2008-2011 update. *Veterinary Dermatology* **24,** 97-117
OLIVRY, T., RIVIERRE, C., JACKSON, H. A., MURPHY, K. M., DAVIDSON, G. & SOUSA, C. A. (2002a) Cyclosporine decreases skin lesions and pruritus in dogs with atopic dermatitis: a blinded randomized prednisolone-controlled trial. *Veterinary Dermatology* **13,** 77-87
OLIVRY, T., RIVIERRE, C. & MURPHY, K. M. (2003a) Efficacy of cyclosporine for treatment induction of canine pemphigus foliaceus. *Veterinary Record* **152,** 53-54
OLIVRY, T., RIVIERRE, C., MURPHY, K. M., JACKSON, H. A. & CHAVEZ, F. (2003b) Maintenance treatment of canine atopic dermatitis with cyclosporin: decreasing dosages or increasing intervals? *Veterinary Dermatology* **14,** 220
OLIVRY, T., STEFFAN, J., FISCH, R. D., PRELAUD, P., GUAGUÈRE, E., FONTAINE, J. & CARLOTTI, D. N. (2002b) Randomized controlled trial of the efficacy of cyclosporine in the treatment of atopic dermatitis in dogs. *Journal of the American Veterinary Medical Association* **221,** 370-377
ORAN, A., MARSHALL, J. S., KONDO, S., PAGLIA, D. & MCKENZIE, R. C. (1997) Cyclosporin inhibits intercellular adhesion molecule-1 expression and reduces mast cell numbers in the asebia mouse model of chronic skin inflammation. *British Journal of Dermatology* **136,** 519-526
PALMEIRO, B. S., MORRIS, D. O., GOLDSCHMIDT, M. H. & MAULDIN, E. A. (2007) Cutaneous reactive histiocytosis in dogs: a retrospective evaluation of 32 cases. *Veterinary Dermatology* **18,** 332-340
PATRICELLI, A. J., HARDIE, R. J. & MCANULTY, J. E. (2002) Cyclosporine and ketoconazole for the treatment of perianal fistulas in dogs. *Journal of the American Veterinary Medical Association* **220,** 1009-1016
PUIGDEMONT, A., BRAZIS, P., ORDEIX, L., DALMAU, A., FUERTES, E., OLIVAR, A., PEREZ, C. & RAVERA, I. (2013) Efficacy of a new topical cyclosporine A formulation in the treatment of atopic dermatitis in dogs. *Veterinary Journal* **197,** 280-285
RADOWICZ, S. N. & POWER, H. T. (2005) Long-term use of cyclosporine in the treatment of canine atopic dermatitis. *Veterinary Dermatology* **16,** 81-86
RADWANSKI, N. E., CERUNDOLO, R., SHOFER, F. S., HANLEY, M. J. & COURT, M. H. (2011) Effects of powdered whole grapefruit and metoclopramide on the pharmacokinetics of cyclosporine in dogs. *American Journal of Veterinary Research* **72,** 687-693
ROSENKRANTZ, W. S. (2004) Pemphigus: current therapy. *Veterinary Dermatology* **15,** 90-98
ROSENKRANTZ, W. S. & ANIYA, J. S. (2007) Cyclosporine, ketoconazole and azathioprine combination therapy in three cases of refractory canine pemphigus foliaceus. *Veterinary Dermatology* **18,** 192
ROSENKRANTZ, W. S., GRIFFIN, C. E. & BARR, R. J. (1989) Clinical evaluation of cyclosporine in animal models with cutaneous immune-mediated disease and epitheliotropic lymphoma. *Journal of the American Animal Hospital Association* **25,** 377-384
RYBNICEK, J., AFFOLTER, V. K. & MOORE, P. F. (1998) Sebaceous adenitis: an immunohistological examination. In Advances in Veterinary Dermatology. Vol 3. Eds K. W. Kwochka, T. Willemse, C. Von Tscharner. Butterworth Heinemann. pp 539-540
SANTORO, D. & CAMPBELL, K. L. (2011) Use of ciclosporin in a dog with canine juvenile sterile granulomatous dermatitis and lymphadenitis. *Veterinary Dermatology* **22,** 287-288
SIHRA, B. S., KON, O. M., DURHAM, S. R., WALKER, S., BARNES, N. C. & KAY, A. B. (1997) Effect of cyclosporin A on the allergen-induced late asthmatic reaction. *Thorax* **52,** 447-452
STEFFAN, J. (2004) Cyclosporine interactions in veterinary medicine: an update. 5th World Congress of Veterinary Dermatology. Proceedings of the Atopica symposium. Vienna. pp 28-32
STEFFAN, J., ALEXANDER, D., BROVEDANI, F. & FISCH, R. D. (2003) Comparison of cyclosporine A with methylprednisolone for treatment of canine atopic dermatitis: a parallel, blinded, randomized controlled trial. *Veterinary Dermatology* **14,** 11-22
STEFFAN, J., FAVROT, C. & MUELLER, R. (2006) A systematic review and meta-analysis of the efficacy and safety of cyclosporin for the treatment of atopic dermatitis in dogs. *Veterinary Dermatology* **17,** 3-16
STEFFAN, J., HORN, J., GRUET, P., STREHLAU, G., FONDATI, A., FERRER, L. & NOLI, C. (2004a) Remission of the clinical signs of atopic dermatitis in dogs after cessation of treatment with cyclosporin A or methylprednisolone. *Veterinary Record* **154,** 681-684
STEFFAN, J., MAURER, M. & ROHLFS, A. (2003) Cyclosporin concentration in the skin following oral administration. *Veterinary Dermatology* **14,** 248
STEFFAN, J., PARKS, C. & SEEWALD, W. (2005) Clinical trial evaluating the efficacy and safety of cyclosporine in dogs with atopic dermatitis. *Journal of the American Veterinary Medical Association* **226,** 1855-1863
STEFFAN, J., STREHLAU, G., MAURER, M. & ROHLFS, A. (2004b) Cyclosporin A pharmacokinetics and efficacy in the treatment of canine atopic dermatitis. *Journal of Veterinary Pharmacology and Therapeutics* **27,** 231-238
TAKAORI, K., NIO, Y., INOUE, K., TUN, T., FUKUMOTO, M., HASHIDA, T., YASUHARA, M., HORI, R. & TOBE, T. (1992) A comparative study on immunosuppressive effects of cyclosporin A and FK 506 on peripheral blood lymphocytes in dogs. *Biotherapy* **4,** 129-137
TAYLOR, A. L., WATSON, C. J. & BRADLEY, J. A. (2005) Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy. *Critical Reviews in Oncology/Hematology* **56,** 23-46
THELEN, A., MUELLER, R. S., LINEK, M., PETERS, S., STECHMANN, K. & STEFFAN, J. (2006) Influence of food intake on the clinical response to cyclosporin A in canine atopic dermatitis. *Veterinary Record* **159,** 854-856
WHALEN, R. D., TATA, P. N., BURCKART, G. J. & VENKATARAMANAN, R. (1999) Species differences in the hepatic and intestinal metabolism of cyclosporine. *Xenobiotica* **29,** 3-9
WISSELINK, M. A. & WILLEMSE, T. (2009) The efficacy of cyclosporine A in cats with presumed atopic dermatitis: a double blind, randomised prednisolone-controlled study. *Veterinary Journal* **180,** 55-59
WON, Y. H., SAUDER, D. N. & MCKENZIE, R. C. (1994) Cyclosporin A inhibits keratinocyte cytokine gene expression. *British Journal of Dermatology* **130,** 312-319
WU, C. Y., BENET, L. Z., HEBERT, M. F., GUPTA, S. K., ROWLAND, M., GOMEZ, D. Y. & WACHER, V. J. (1995) Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clinical Pharmacology and Therapeutics* **58,** 492-497