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.

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), 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 Brunner 2005 Guaguère and others 2004 Takaori and others 1992 Bussmann 2009 |
| Antigen presenting cells (APCs) | Reduces both the number and activity of APCs, especially Langerhans cells | Cirillo and others 1990 |
| Basophils          | Reduces degranulation, cytokine secretion, chemotaxis and longevity                          | Cesal and Davila 2001 Sihra and others 1997 |
| Eosinophils        | Reduces degranulation, cytokine secretion, chemotaxis and longevity                          | Creagh and others 1995 Cockerill and others 1995 |
| Endothelial cells  | Reduces adhesion molecule expression                                                         | Baumer and Kietzmann 2007 Won and others 1994 |
| Keratinocytes      | Anti-proliferative effect and reduced cytokine production                                   | Brazis and others 2006 Hatfield and Rothen 1992 Tran and others 1997 |
| Mast cells         | Reduces numbers, histamine release and cytokine production (IL-3, 4, 5, 8, TNF)             | GM-CSF Granulocyte macrophage colony stimulating factor, IFN Interferon, IL Interleukin, NF-AT Nucleic factor of activated T cells, TNF Tumour necrosis factor |

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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 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 cytochrome p450 3A (CYp3A) enzymes also within the intestines (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 2004). The drug is metabolised mainly within the intestines (Whalen and others 1999). The bioavailability of the drug by cytochrome P450 3A (CYP3A) enzymes 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).

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: 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) | 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=0.001 >50% improvement in 69% cases No difference between CsA and prednisolone treated groups | Significant improvement in CsA treated group P=0.003 >50% improvement in 77% cases No difference between CsA and prednisolone treated groups | A3 | Olivry and others 2002b |
| 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 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 (59%), MP (38%) | 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 CADERI 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 | Besnognor 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 lesion scores after 6 weeks 44% CsA treated and 53% glucocorticoid-treated dogs achieved ≥50% reduction in lesion 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 38% CsA treated and 49% glucocorticoid-treated dogs achieved ≥50% reduction in pruritus after 6 weeks | A1 | Olivry 2004 |
| Glucocorticoids (74) | CsA (132) | 50% reduction in pruritus 15/31 cases treated with CsA 5 mg/kg after 6 weeks | 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 | Radwicz and Power 2005 |
| CS            | CsA 5 mg/kg for at least six months (51) | | | | | |
Research

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 one study in healthy beagles showed that ketoconazole at 5 mg/kg sid for 7 days then 1 mg/kg eod for 35 days (7) No difference between two groups after 6 weeks

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 in 45% CsA and 7% placebo cases after 8 weeks | 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        | Stefan 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        | Stefan and others 2005 |
| MET           | Placebo (160) Oral glucocorticoids (74) Antihistamines (23) | 672 CsA treated (672): 5 mg/kg (642), 2.5 mg/kg (30) | 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        | Stefan and others 2006 |
| RCT-NB        | CsA 5 mg/kg administered with food (15) CsA 5 mg/kg 2 hours before or after feeding (10) | 799 dogs in total | No difference between two groups at any time point to 6 months | No difference between two groups | B3        | Thelen and others 2006 |
| RCT-DB        | Virbagen Omega (V0) 10 injections of Rituxan (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 V0 expipient (8) | Significant reduction in lesions over baseline in both groups P=0.0001 ≥50% reduction in CADESI scores in 87.5% CsA treated cases after 8 weeks | Significant reduction in pruritus in both groups over baseline after 8 weeks (PICAD scoring) P=0.001 ≥50% reduction in pruritus (PICAD) in 87.5% CsA treated cases after 8 weeks | A4        | Carlotti and others 2009 |
| RCT-DB        | Prednisolone 1 mg/kg 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 | A4        | Kovalk and others 2011 |
| RCT-DB        | Hydrocortisone in capsules 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) Nanoparticles CsA spray on formulation (17) | Leslie 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 | Owner assessment of success in 48 to 67% of pets | A3        | Pugdemont 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

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 215.5 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. Metoclopramide 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
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 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 (Steinberg 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 others 2015). 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-
ation 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% reduction in pruritus in the treatment group compared to 28.6% 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, fluorescence 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.

Long-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.
The page contains a table titled **Table 5: Evidence for efficacy of ciclosporin (CsA) in miscellaneous skin diseases**. The table lists various skin diseases along with the type of study, treatment, and level of evidence. The table is structured as follows:

| Disease                                                      | Type of study (number of dogs) | Treatment                                                                 | Efficacy – lesions                                                                 | Level of evidence |
|--------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------|
| 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                |
| 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                |
| Juvenile cellulitis                                           | CR (1)                         | Refractory to topical and systemic dexamethasone                         | 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                |
| Sterile nodular panniculitis and vasculitis                  | CR (1)                         | Prednisolone 0.5 mg/kg sid CsA 5 mg/kg sid                              | Excellent response after 20 weeks                                                | D4                |
| Sterile nodular panniculitis                                 | CS (2)                         | CsA 5 mg/kg                                                              | 80% improvement after 2 weeks Complete resolution after 6 weeks                 | D4                |
| 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 increased to daily therapy. | D4                |
| 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                |
| Vascular cutaneous lupus erythematosus                       | 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 6 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 to 1/5 Lesions recurred in 3/5 cases after cessation of CsA. Further resolution when CsA restarted CsA reduced prednisolone dosage required. | D4                |
| 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                |
| 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                |
| Uveodermatologic syndrome                                    | CR (1)                         | CsA 4.7 mg/kg/sid Prednisolone 0.2 mg/kg bid (22 days)                   | Skin lesions controlled over 10 month period                                      | D4                |
| Pyoderma gangrenosum                                         | CR (1)                         | CsA 5 mg/kg/sid Prednisolone 0.2 mg/kg bid (22 days)                     | Complete resolution after 8 weeks                                                | D4                |
| Proliferative infundibular mural folliculitis and dermatitis (Labrador retrievers) | CS (4) | CsA 5 to 6.2 mg/kg/sid in 3 dogs Prednisolone 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                |
| 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                |
| 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                |

*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

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**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

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.
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 ear infections 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 crusty 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 (Olviry and others 2002a), 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 beameliorated 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.

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