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). 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

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Mode of action of ciclosporin</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cells</td>
<td>Inactivation of NF-AT and reduced IL-2 production which suppresses T cells and T cell cytokine production (IL-4, 5, 6, 8, 13)</td>
<td>Bunikowski and others 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ho and others 1996</td>
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<td></td>
<td></td>
<td>Matsuda and Koyasu 2000</td>
</tr>
<tr>
<td>B cells</td>
<td>Inhibits growth and activation of B cells. Minimal inhibition of antibody production or humoral response to vaccines in dogs</td>
<td>Brazis and others 2006</td>
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<td></td>
<td></td>
<td>Bruner 2005</td>
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<td></td>
<td></td>
<td>Guaguère and others 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Takaori and others 1992</td>
</tr>
<tr>
<td>Antigen presenting cells (APCs)</td>
<td>Reduces both the number and activity of APCs, especially Langerhans cells</td>
<td>Bussmann 2009</td>
</tr>
<tr>
<td>Basophils</td>
<td>Reduces degranulation, cytokine secretion, chemotaxis and longevity</td>
<td>Cicirillo and others 1990</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Reduces degranulation, histamine release and leukotriene synthesis</td>
<td>Marsella and Olvy 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sihra and others 1997</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>Reduces adhesion molecule expression</td>
<td>Cockrell and others 1995</td>
</tr>
<tr>
<td>Keratinocytes</td>
<td>Anti-proliferative effect and reduced cytokine production</td>
<td>Baumer and Kietzmann 2007</td>
</tr>
<tr>
<td>Mast cells</td>
<td>Reduces numbers, histamine release and cytokine production (IL-3, 4, 5, 8, TNF)</td>
<td>Won and others 1994</td>
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<tr>
<td></td>
<td></td>
<td>Brazis and others 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hatfield and Roehm 1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oran and others 1997</td>
</tr>
</tbody>
</table>

Ciclosporin is a lipophilic cyclic polypeptide with powerful immunosuppressive and immunomodulatory properties that is isolated from the fungus Beauveria nova (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 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.

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

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Ciclosporin is known to interact with a wide range of pharmacological agents. These interactions have been well researched in people but 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 of efficacy of ciclosporin (CsA) in canine atopic dermatitis

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Control group (number of dogs)</th>
<th>Treatment group (number of dogs)</th>
<th>Efficacy – lesions</th>
<th>Efficacy – pruritus</th>
<th>Level of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>CS A 5 mg/kg (14)</td>
<td>Median lesion reduction 60% (after 2 weeks)</td>
<td>Median pruritus reduction 100% (after 2 weeks)</td>
<td>Owner perceived efficacy excellent in 9/14 dogs</td>
<td>C3 Fontaine and Olivry 2001</td>
<td></td>
</tr>
<tr>
<td>RCT-DB</td>
<td>Prednisolone 0.5 mg/kg (15)</td>
<td>CsA 5 mg/kg (15)</td>
<td>Significant improvement in CsA treated group P&lt;0.0001 &gt;50% improvement in 69% cases No difference between CsA and prednisolone treated groups</td>
<td>Significant improvement in CsA treated group P&lt;0.0001 &gt;50% improvement in 77% cases No difference between CsA and prednisolone treated groups</td>
<td>A3 Olivry and others 2002a</td>
<td></td>
</tr>
<tr>
<td>RCT-DB</td>
<td>Placebo (30) CsA 2.5 mg/kg sid (30)</td>
<td>CsA 5 mg/kg (31)</td>
<td>Significant improvement in CsA (5 mg/kg sid) treated group compared to both control groups P&lt;0.002 ≥50% reduction in lesion scores 22/31 cases treated with CsA 5 mg/kg after 6 weeks</td>
<td>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</td>
<td>A2 Olivry and others 2002b</td>
<td></td>
</tr>
<tr>
<td>RCT-SB</td>
<td>Methylprednisolone (MP) (9.5 mg/kg) (59)</td>
<td>CsA 5 mg/kg (117)</td>
<td>Improvement over baseline after 8 weeks CsA group (53%); MP group (45%) No difference between groups</td>
<td>Owner pruritus scores improvement over baseline after 8 weeks CsA (59%); MP (38%) No difference between groups</td>
<td>A1 Steffan and others 2003</td>
<td></td>
</tr>
<tr>
<td>RCT-NB</td>
<td>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)</td>
<td>Significant improvement in 41/41 dogs P&lt;0.001 after 6 weeks</td>
<td>Significant improvement in 36/41 dogs P&lt;0.00 after 6 weeks</td>
<td>Overall 27% reduction in pruritus over baseline scores after 4 weeks (owners assessment)</td>
<td>C2 Burton and others 2004</td>
<td></td>
</tr>
<tr>
<td>RCT-SB</td>
<td>CsA 5 mg/kg (41)</td>
<td>20% dogs showed ≥50% reduction in lesion scores after 4 weeks (investigators assessment)</td>
<td>30% dogs with ≥50% reduction in pruritus after 4 weeks (owner assessments)</td>
<td>No difference between groups after 12 weeks</td>
<td>C3 Bensignor and Guaguère 2004 (from Steffan and others 2006)</td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>Placebo (164) CsA (165)</td>
<td>50% CsA treated vs 12% placebo treated dogs achieved ≥50% reduction in lesion scores after 6 weeks</td>
<td>38% CsA treated vs 19% placebo treated dogs achieved a level of mild pruritus (&lt;3/5 pruritus score) after six weeks</td>
<td>Significant improvement in CsA treated and 49% glucocorticoids-treated dogs achieved ≥50% reduction in pruritus after 6 weeks</td>
<td>A1 Olivry 2004</td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>CsA 5 mg/kg for at least six months (51)</td>
<td>44% CsA treated and 53% glucocorticoid-treated dogs achieved ≥50% reduction in lesion scores after 6 weeks</td>
<td>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)</td>
<td>No difference between CsA and prednisolone treated groups</td>
<td>D1 Radowicz and Power 2005</td>
<td></td>
</tr>
</tbody>
</table>

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 microemulsion (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 (Necoral; 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 2004) and the datasheet recommendation 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 (Ehre 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 2008), further supporting once daily dosing.
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 therapeutically effective 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 35 per cent respectively to still achieve similar blood concentration levels (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 2006). The interaction between ciclosporin and cimetidine, an H2 receptor antagonist and a potent inhibitor of the CYP 3A system, has been studied in dogs (Daigne and others 2001). This work demonstrated that cimetidine delayed but did not decrease the rate of absorption of ciclosporin. Metaclopamide has been shown to have no effect on the pharmacokinetic parameters of ciclosporin in healthy dogs (Radowanski 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 2: cont'd

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Control group (number of dogs)</th>
<th>Treatment group (number of dogs)</th>
<th>Efficacy – lesions</th>
<th>Efficacy – pruritus</th>
<th>Level of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT-DB</td>
<td>Placebo (soybean oil) (134)</td>
<td>CsA 5 mg/kg (134)</td>
<td>Mean CADESI score CsA treated group after 4 weeks significantly lower than baseline and placebo group P&lt;0.001 50% reduction in CADESI scores in 68% cases after 8 weeks</td>
<td>Mean owner pruritus score CsA treated group after 4 weeks significantly lower than baseline and placebo group P&lt;0.001 % dogs with severe pruritus scores decreased from 64% to 15% after 8 weeks</td>
<td>A1</td>
<td>Stefan and others 2005</td>
</tr>
<tr>
<td></td>
<td>Open</td>
<td>CsA 5 mg/kg (266)</td>
<td>+50% reduction in CADESI scores in 68% cases after 8 weeks</td>
<td>% dogs with severe pruritus scores decreased from 64% to 15% after 8 weeks</td>
<td>C1</td>
<td>Stefan and others 2005</td>
</tr>
<tr>
<td>MET</td>
<td>Placebo (160) Oral glucocorticoids (74) Antihistamines (23)</td>
<td>672 CsA treated (672): 5 mg/kg (642), 2.5 mg/kg (30)</td>
<td>Lesion scores improved from baseline by 53 to 84% after 6 weeks</td>
<td>After 4 to 6 weeks treatment +50% reduction in pruritus over baseline in 35% to 67% of cases</td>
<td>A1</td>
<td>Stefan and others 2006</td>
</tr>
<tr>
<td>RCT-NB</td>
<td>CsA 5 mg/kg administered with food (15) CsA 5 mg/kg 2 hours before or after feeding (10)</td>
<td>799 dogs in total</td>
<td>No significant difference in lesions over baseline in both groups p&gt;0.0001</td>
<td>44% dogs had +50% reduction in pruritus after 4 weeks</td>
<td>B3</td>
<td>Thelen and others 2006</td>
</tr>
<tr>
<td>RCT-DB</td>
<td>Virbagen Omega (V0) 10 injections of rFeIFN-α (1 to 5 million units according to bodyweight) over 6 months and placebo CsA-like capsules (18)</td>
<td>CsA 5 mg/kg sid for 2 months and then twice weekly for 4 months + placebo injections of V0 except (8)</td>
<td>Significant reduction in lesions over placebo in both groups p=0.0001 +50% reduction in CADESI scores in 68.5% CsA treated cases after 8 weeks</td>
<td>Significant reduction of pruritus in both groups over baseline after 8 weeks (PICAD scoring) P&lt;0.001 +50% reduction in pruritus (PICAD) in 87.5% CsA treated cases after 8 weeks</td>
<td>A4</td>
<td>Carlotti and others 2009</td>
</tr>
<tr>
<td>RCT-SB</td>
<td>Prednisolone 1 mg/ kg sid for 7 days then 1 mg/kg eod for 28 days (7)</td>
<td>CsA 5 mg/kg sid (human generic form) (13)</td>
<td>11/13 CsA treated and 6/7 prednisolone treated dogs had a +50% reduction in CADESI score after 6 weeks No difference between two groups at any time point to 6 months</td>
<td>10/13 CsA treated, and 6/7 prednisolone treated dogs had +50% reduction in pruritus scores (investigator assessment) after 6 weeks</td>
<td>A4</td>
<td>Kovalek and others 2011</td>
</tr>
<tr>
<td>RCT-DB</td>
<td>Hydrocortisone aceponate 0.585% (HCA) applied topicaly once daily (25)</td>
<td>CsA 5 mg/kg (23)</td>
<td>Significant improvement in both groups P&lt;0.0001 +50% reduction in CADESI after 8 days in 86.7% CsA and 75% HCA groups No difference between groups</td>
<td>Significant improvement in both groups P&lt;0.0001 +50% reduction in pruritus after 84 days in 57.1% CsA and 66.6% HCA groups No difference between groups</td>
<td>A2</td>
<td>Nuttall and others 2012</td>
</tr>
<tr>
<td>RCT-NB</td>
<td>CsA 5 mg/kg sid and prednisolone 1 mg/kg sid for 7 days then eod for 14 days (23)</td>
<td>CsA 5 mg/kg sid (25)</td>
<td>Mean reduction in CADESI in CsA and CsA + prednisolone treated groups after 28 days was 56.52% and 57.9% respectively The difference between groups was not significant</td>
<td>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</td>
<td>B2</td>
<td>Dip and others 2013</td>
</tr>
<tr>
<td>RCT-DB</td>
<td>Placebo spray (15) Nanocapsule CsA spray on formulation (17)</td>
<td>Nanocapsule CsA spray on formulation (17)</td>
<td>Lesion score significantly lower in treatment compared baseline after 21 and 45 days P&lt;0.01 No significant improvement in placebo group after 21 and 45 days</td>
<td>64% of treatment group had a +50% reduction in pruritus compared to 11% in placebo group after 45 days</td>
<td>A3</td>
<td>Pudgemont and others 2013</td>
</tr>
</tbody>
</table>

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 binding and/or randomisation; C Open trial with no control; D Case series, case report, anecdotal report etc.

1>50 dogs/group, 2>50 dogs/group, 3>10 to 50 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 blind, 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 (B4)
Research

Table 3: Evidence of efficacy of ciclosporin (CsA) in peripheral fistulization

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Treatment and control groups (number of dogs)</th>
<th>Efficacy – lesions</th>
<th>Level of evidence*</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT-DB</td>
<td>CsA 5 mg/kg bid for 16 weeks (10) Placebo for 4 weeks then CsA 5 mg/kg bid for 12 weeks (10)</td>
<td>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</td>
<td>A3</td>
<td>Matthews and Sukhiani 1997</td>
</tr>
<tr>
<td>CS</td>
<td>CsA 7.5 mg/kg bid with food (6)</td>
<td>Reduction in lesion size of 52 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</td>
<td>D4</td>
<td>Griffiths and others 1999</td>
</tr>
<tr>
<td>Open</td>
<td>CsA 1 mg/kg and ketoconazole 10 mg/kg sid (16)</td>
<td>13/16 dogs had complete resolution of lesions after 16 weeks 7/16 remained in remission for &gt;12 months Recurrence seen in three dogs at 8, 10 and 12 months after treatment, and in three dogs within 1 month of treatment</td>
<td>C3</td>
<td>Mouatt 2002</td>
</tr>
<tr>
<td>Open</td>
<td>CsA 2.5 mg/kg bid (8) CsA 4 mg/kg sid (4) All 12 also ketoconazole 8 mg/kg sid</td>
<td>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</td>
<td>C3</td>
<td>Patricelli and others 2002</td>
</tr>
<tr>
<td>Open</td>
<td>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</td>
<td>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 5/6 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</td>
<td>C4</td>
<td>Doust and others 2003</td>
</tr>
<tr>
<td>Open</td>
<td>CsA 0.5, 0.75, 1 or 2 mg/kg/bid, ketoconazole 5.3 to 8.9 mg/kg bid (19)</td>
<td>Complete resolution of lesions in 19/19 dogs in 3 to 10 weeks In 18/19 cases lesions resolved in 56 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</td>
<td>C3</td>
<td>O’Neill and others 2004</td>
</tr>
<tr>
<td>Open</td>
<td>CsA 4 mg/kg bid until 2 weeks past lesion resolution or until no further improvement after 4 weeks (26)</td>
<td>25/26 improved Follow up was 1 to 20 months (mean 6.8 months) 18/26 had complete resolution. Of these, 6 recur 7/26 improved but underwent surgery resection of residual lesions. Of these, 3 recur Recurrence of lesions in 1 to 32 weeks (mean 10.4 weeks)</td>
<td>C2</td>
<td>Hardie and others 2005</td>
</tr>
<tr>
<td>CS</td>
<td>CsA 2.5 to 5 mg/kg bid (7) CsA 1 to 1.5 mg/kg bid combined with ketoconazole 12.5 mg/kg bid (11) Azathioprine 1 to 2 mg/kg bid 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</td>
<td>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</td>
<td>D4</td>
<td>Klein and others 2006</td>
</tr>
<tr>
<td>RCT-SB</td>
<td>CsA 2 mg/kg/sid (10) CsA 5 mg/kg/sid (10)</td>
<td>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</td>
<td>A3</td>
<td>House and others 2006</td>
</tr>
</tbody>
</table>

* 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

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-
loration has been developed to enhance penetration with the view to topical therapy. The use of this product in a six-week RCT of 52 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), 56 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.

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.
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 population (Brandt and others 2009) suggesting that ciclosporin therapy has been shown to significantly increase the T regulatory cell population (Keppel and others 2008).

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of study (number of dogs)</th>
<th>Treatment</th>
<th>Efficacy – lesions</th>
<th>Level of evidence*</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canine cutaneous and systemic histiocytosis</td>
<td>CS (44)</td>
<td>3 dogs with systemic histiocytosis treated with CsA. Dosage not given</td>
<td>Good therapeutic success in 3/3 dogs treated with CsA</td>
<td>D4</td>
<td>Aflorter and Moore 2000</td>
</tr>
<tr>
<td>Cutaneous reactive histiocytosis</td>
<td>CS</td>
<td>1 dog treated with ketoconazole 10 mg/kg and CsA 4 mg/kg/kg in one dog, dosage not given for other dog</td>
<td>Complete resolution of lesions in 67 days for one dog; not given for the other dog Both dogs maintained on combination of ketoconazole/CsA</td>
<td>D4</td>
<td>Palmeiro and others 2007</td>
</tr>
<tr>
<td>Juvenile cellulitis</td>
<td>CR (1)</td>
<td>Refractory to topical and systemic dexamethasone</td>
<td>Marked improvement after 4 weeks. Lymphadenopathy persisted and CsA increased to 10 mg/kg/kg 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</td>
<td>D4</td>
<td>Santoro and Campbell 2011</td>
</tr>
<tr>
<td>Sterile nodular panniculitis and vasculitis</td>
<td>CR (1)</td>
<td>Prednisolone 0.5 mg/kg sid CsA 5 mg/kg/kg</td>
<td>Excellent response after 20 weeks</td>
<td>D4</td>
<td>Bandreux and others 2011</td>
</tr>
<tr>
<td>Sterile nodular panniculitis</td>
<td>CS (2)</td>
<td>CsA 5 mg/kg</td>
<td>80% improvement after 2 weeks Complete resolution after 6 weeks</td>
<td>D4</td>
<td>Guagliuie 2000</td>
</tr>
<tr>
<td>Focal metatarsal sinus tracts</td>
<td>CR (1)</td>
<td>CsA 5 mg/kg for 2 months</td>
<td>Complete resolution after 2 months Recurrence when dosage reduced to 5 mg/kg/kg then further resolution increased to daily therapy</td>
<td>D4</td>
<td>Oliveira and others 2011</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>CS (5)</td>
<td>CsA 5 to 10 mg/kg/kg for 1 to 3 months</td>
<td>Lesion scores worsened in 4/5 dogs CsA was ineffective as a sole agent when used at these doses to treat canine pemphigus foliaceus</td>
<td>D4</td>
<td>Olivy and others 2003</td>
</tr>
<tr>
<td>Vascular cutaneous lupus erythematosus</td>
<td>CS (5)</td>
<td>Prednisolone 1 to 2.6 mg/kg/kg/adapted over 20 to 36 weeks to 0.5 mg/kg/kg CsA 5 to 18 mg/kg/kg for 8 to 39 months then tapered to 3 to 4 mg/kg/kg/ad for resolution of lesions CsA administered as maintenance for 1 to 18 months</td>
<td>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</td>
<td>D4</td>
<td>Maeda and others 2008</td>
</tr>
<tr>
<td>Exfoliative cutaneous lupus erythematosus</td>
<td>CR (1)</td>
<td>CsA 4 mg/kg/kg Prednisolone 0.2 mg/kg/kg (for 22 days)</td>
<td>Complete resolution after 2 months Recurrence when dosage reduced to 5 mg/kg/kg then further resolution increased to daily therapy</td>
<td>D4</td>
<td>Font and others 2006</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>CS (6)</td>
<td>Four dogs treated with CSA 5 to 10 mg/kg/kg/adapted over 20 to 36 weeks to 0.5 mg/kg/kg CsA 5 to 18 mg/kg/kg for 8 to 39 months then tapered to 3 to 4 mg/kg/kg/ad for resolution of lesions CsA administered as maintenance for 1 to 18 months</td>
<td>All cases in remission after 10 to 18 months It was possible to withdraw glucocorticoids 3 to 12 weeks after addition of CsA</td>
<td>D4</td>
<td>Mauldin and others 2010</td>
</tr>
<tr>
<td>Uveodermatologic syndrome</td>
<td>CR (1)</td>
<td>CsA 4.7 mg/kg/kg Prednisolone 0.6 mg/kg/kg/adapted over 20 to 36 weeks to 0.5 mg/kg/kg CsA 5 to 18 mg/kg/kg for 8 to 39 months then tapered to 3 to 4 mg/kg/kg/ad for resolution of lesions CsA administered as maintenance for 1 to 18 months</td>
<td>All cases in remission after 10 to 18 months It was possible to withdraw glucocorticoids 3 to 12 weeks after addition of CsA</td>
<td>D4</td>
<td>Noli and Toma 2006</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>CR (1)</td>
<td>CsA 5 mg/kg/kg Prednisolone 0.2 mg/kg/kg (for 22 days)</td>
<td>Complete resolution after 2 months Recurrence when dosage reduced to 5 mg/kg/kg then further resolution increased to daily therapy</td>
<td>D4</td>
<td>Blackwood and others 2011</td>
</tr>
<tr>
<td>Proliferative infundibular mural folliculitis and dermatitis (labrador retrievers)</td>
<td>CS (4)</td>
<td>CsA 5 to 6.2 mg/kg/kg in 3 dogs Prednisolone 0.65 to 2 mg/kg/kg, Aza 1.5 to 2.5 mg/kg/kg, Csa 1.5 to 2.5 mg/kg/kg, Ketoconazole 2.5 to 5 mg/kg/kg</td>
<td>Rapid response to ciclosporin in all cases Two dogs remained in remission for at least 7 and 8 months after discontinuation of therapy</td>
<td>D4</td>
<td>Hargis and others 2013</td>
</tr>
<tr>
<td>Idiopathic chronic pododermatitis</td>
<td>Open (13)</td>
<td>Prednisolone 2 mg/kg/kg CsA 5 mg/kg/kg</td>
<td>Marked clinical improvement over 2 to 8 weeks</td>
<td>D4</td>
<td>Breathnach and others 2005</td>
</tr>
<tr>
<td>End stage proliferative otitis externa</td>
<td>CS (5)</td>
<td>CsA 5 mg/kg/kg</td>
<td>Significant clinical improvement and improved quality of life</td>
<td>D4</td>
<td>Hall and others 2003</td>
</tr>
</tbody>
</table>

* See footnote to Table 2

**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. 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 (Patrielli 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 epitheliotropic cutaneous lymphoma (Rosenkranz and others 1989).

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 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 (Rosenkranz 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 2003). 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 (Rosenkranz 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.

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Ciclosporin 10 years on: indications and efficacy

Peter Forsythe and Sue Paterson

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