Review

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Life-long diseases need life-long treatment: long-term safety of ciclosporin in canine atopic dermatitis

Tim Nuttall, Douglas Reece, Elizabeth Roberts

Ciclosporin (Atopica; Novartis Animal Health) has been licensed for canine atopic dermatitis (AD) since 2002. Adverse events (AEs) have been reported in 55 per cent of 759 dogs in 15 clinical trials, but are rare in pharmacovigilance data (71.81 AEs/million capsules sold). Gastrointestinal reactions were most common, but were mild and rarely required intervention. Other AEs were rare (≤1 per cent in clinical trials; <10/million capsules sold). Hirsutism, gingival hyperplasia and hyperplastic dermatitis were rarely significant and resolved on dose reduction. Ciclosporin decreases staphylococcal and *Malassezia* infections in AD, and at the recommended dose is not a risk factor for other infections, neoplasia, renal failure or hypertension. The impact on glucose and calcium metabolism is not clinically significant for normal dogs. Concomitant treatment with most drugs is safe. Effects on cytochrome P450 and MDR1 P-glycoprotein activity may elevate plasma ciclosporin concentrations, but short-term changes are not clinically significant. Monitoring of complete blood counts, urinalysis or ciclosporin levels is not justified except with higher than recommended doses and/or long-term concurrent immunosuppressive drugs. Ciclosporin is not a contraindication for killed (including rabies) vaccines, but the licensed recommendation is that live vaccination is avoided during treatment. In conclusion, ciclosporin has a positive risk-benefit profile for the long-term management of canine AD.

CICLOSPORIN (ciclosporine, cyclosporine, cyclosporin A or CsA) is a cyclic oligopeptide macrolide that inhibits cytoplasmic calcineurin phosphatase (Steffan and others 2006). Ciclosporin blocks induction of genes for a variety of cytokines and cytokine receptors, resulting in immunomodulating activity. Its effects on cytokines involved in the activation, proliferation and survival of cells important in cutaneous immunity and allergic reactions, including Langerhans' cells, lymphocytes, mast cells and eosinophils, led to interest in using it to manage canine atopic dermatitis (AD). A small open study showing efficacy in reducing clinical lesions and pruritus was published in 2001 (Fontaine and Olivry 2001). Since then there have been numerous other studies from the USA, Europe, Japan and Australia. Ciclosporin was licensed for the management of canine AD in 2002 as Atopica (Novartis Animal Health) and is now approved and available in 23 countries worldwide. In 2006, a meta-analysis of 10 studies, including 799 dogs, concluded that oral ciclosporin was as effective as systemic glucocorticoids (Steffan and others 2006). Other meta-analyses and systematic reviews have also confirmed that ciclosporin is highly effective in the treatment of canine AD (Olivry and Mueller 2003, Olivry and others 2010a, Olivry and Bizikova 2013), and the 2010 International Task Force for Canine Atopic Dermatitis (now the International Committee for Allergic Diseases in Animals [ICADA]) practice guidelines for the treatment of canine AD specifically recommended ciclosporin in the management of chronic AD (Olivry and others 2010b).

Canine AD is a disease of young animals, with the peak age of onset between six months and three years (Favrot and others 2010). It is a chronic relapsing condition and most dogs will require ongoing, usually life-long, therapy. It is therefore important to understand the long-term safety of therapeutic interventions to balance efficacy and adverse effects in order to maintain a good quality of life. Safety data for registration usually only includes clinical trial data from relatively small numbers of dogs treated for weeks to months. Therefore, the monitoring of the safety and efficacy of marketed medicines through pharmacovigilance (PV) is an essential and efficacious tool to assess a drug's safety and efficacy profile. Adverse effects that occur at low rates, have a breed predilection or drug:drug interactions may not be evident during clinical trial investigation. For PV purposes, adverse effects are any side effect, injury, toxicity or sensitivity reaction associated with use of an animal drug, whether or not considered to be drug related and whether or not the drug was used in accordance with the approved labelling, and can include product reports of failure to perform as expected.

In the 10 years or so that Atopica has been available an estimated 142 million doses of ciclosporin have been sold (Roberts and others 2012a). This provides a wealth of experience and data on the safety of ciclosporin in dogs with AD. The aim of this review is to ana-

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lyse published papers and PV data to report the prevalence of adverse effects associated with ciclosporin treatment. This data will be useful to clinicians when discussing treatment options with the owners of atopic dogs.

Analysis of adverse effects associated with ciclosporin treatment

A wide variety of adverse effects have been associated with ciclosporin treatment. This review discusses these effects grouped by body system and/or tissue in more detail, reviewing the strength of association with ciclosporin and the relative risk. This review is complicated by the variety of different reports that include PV data, experimental studies, single case studies, clinical trials, meta-analyses and systematic reviews. In particular, it is difficult to determine the significance of adverse effects where there is no control group to permit case-control analysis and calculation of risk. This confounding by indication creates a bias in the PV dataset as the indication for treatment (atopic dermatitis) may be related to a higher prevalence of specific adverse events in a ciclosporin treatment group than one would see in a control group or the general population. Data from single case reports may be limited, as the report may be spontaneous, confounded by the presence of unrelated disease or concomitant therapy such that the association is speculative. A plausible association with ciclosporin can be made where there is a valid link between drug exposure and an adverse drug reaction (ADR), such as when an ADR occurs early in treatment and resolves with reduction of the dose or cessation of therapy. However, it can be difficult to confirm causality as dogs may have concurrent treatment or conditions that could also explain the observed clinical signs.

Establishing a valid link between drug exposure and an ADR is based on detailed medical and drug history, but there are no specific diagnostic criteria. Several methods (eg, Naranjo scale, ABON system, RUCAM method, modified Kramer algorithm and others) have been used to determine the causality association or assessment of an ADR. Unfortunately, very few published veterinary reports use these scores for evaluation.

It is also important to note that the analysis of adverse events and development of a risk-benefit profile for a product to treat a non-life threatening condition would be considered acceptable for a high prevalence of mild adverse events, but would be unacceptable for a low prevalence of severe adverse effects.

Adverse effects associated with ciclosporin treatment for canine atopic dermatitis

This article has analysed and reviewed data from peer-reviewed studies and published clinical trials reporting the outcomes of treatment of canine AD at standard doses (ie, a starting dose of approximately 5 mg/kg once daily, tapered to clinical effect) of ultramicronised emulsified ciclosporin administered orally (Atopica). Unpublished studies, experimental studies in healthy dogs, studies in other species, and off-label use in other conditions, at other doses and/or combined with other medication were not included in the analysis but have been quoted where appropriate when discussing the likely significance of certain adverse effects. The review of PV data included off-label use in other conditions, at other doses and/or treatment combined with other medication.

This resulted in a meta-analysis of data from 15 studies including 759 dogs. All but one study used oral ultramicronised emulsified ciclosporin as Atopica; the exception used a generic ultramicronised emulsified ciclosporin (Equoral; Teva Pharmaceuticals) (Kovalik and others 2011a). The findings are summarised in Table 1, which reports findings of all dogs that had at least one adverse event reported. This is an approximation of the true figures, as it was not always clear whether some dogs had more than one adverse event (and therefore were counted more than once) and some dogs had multiple episodes of the same adverse event (which only counted once). Finally, adverse events that were clearly unrelated to treatment were disregarded (eg, road traffic accidents, cruciate injuries, foreign bodies, etc). Pharmacovigilance data (Roberts and others 2012a) was reviewed in light of the meta-analysis for consistency and completeness (Table 2).

At least one adverse event was reported in 420 of 759 treated dogs (55 per cent, with a range of 0 to 88 per cent among the individual studies). However, the majority of these were mild and self-limiting requiring cessation of treatment in only 4 per cent of cases (range 0 to 17 per cent). The most frequent adverse events were gastrointestinal (51 per cent; range 0 to 60 per cent), which is consistent with the PV data, and other problems were seen in no more than 1 per cent of treated dogs. There was considerable variation between studies, which probably reflects the number of dogs and duration of treatment. There was also some variation in terminology of recording the adverse events (eg, between different gastrointestinal and urinary tract clinical signs). In addition, there may have been differences in how each study asked for and recorded possible adverse events. Non-clinically significant changes in haematology, biochemistry and other parameters were not recorded as individual adverse events but mean values and changes, where available, are discussed later.

Gastrointestinal adverse effects

Gastrointestinal upsets are the most common adverse effects associated with ciclosporin. They occurred in 46 per cent of the 759 dogs included in Table 1, and were the only ADRs consistently reported in most studies. Table 2 shows that the top two clinical signs reported to PV also included signs of gastrointestinal upset (eg, vomiting and diarrhoea). In another meta-analysis of 672 atopic dogs treated with ciclosporin, gastrointestinal problems were recorded in 306 (45 per cent) of dogs, whereas other adverse effects were seen in less than 2.1 per cent (Steffan and others 2006). However, these figures could have overestimated the prevalence of gastrointestinal upsets as individual dogs were reported to have had multiple events. Vomiting, reported in 25 to 31 per cent of dogs, was three to four times more likely in ciclosporin-treated dogs compared to controls. Soft stools, diarrhoea and/or other problems affected 18 to 20 per cent of the ciclosporin-treated dogs, roughly twice the proportion of the control groups (Table 1) (Steffan and others 2006). The incidence appears to be dose-related, and may involve reversible microvilli damage caused by excipients in the oral microemulsified formulation (Nerurkar and others 1996).

Most of the gastrointestinal upsets appeared to be mild, with repeated or prolonged episodes of vomiting or other problems rarely reported (Steffan and others 2006). Two studies specifically reported the number of gastrointestinal disturbances per dog (Olivry and others 2002a, Steffan and others 2005). Of the dogs with at least one gastrointestinal adverse effect, 53 per cent to 73 per cent vomited one to three times over three months, with most episodes recorded in the first month of treatment. Only 10 per cent of dogs had multiple sporadic episodes of vomiting and vomiting was considered severe in only 1 per cent of cases (Steffan and others 2005). The incidence of soft stools or diarrhoea was similar to that of vomiting (Olivry and others 2002a, Steffan and others 2005). In the largest study, diarrhoea was seen in 53 of 266 dogs (20 per cent), and was associated with vomiting in 10 dogs. Most cases were seen in the first month of treatment (Steffan and others 2005), resolved without treatment in all but two dogs, and were considered severe in only one dog. Single episodes were seen in 43 per cent of dogs, while multiple episodes were reported in 28 per cent. Most episodes were self-limiting, with clinical signs for seven days or more reported in only 13 per cent of dogs. Loss of appetite was only seen in 2 per cent of treated dogs (Table 1) (Steffan and others 2006), where it was usually associated with vomiting or diarrhoea (Steffan and others 2005). Weight loss has been seen in <1 per cent of dogs (Steffan and others 2006); in one study only one of 266 dogs experienced weight loss and this was associated with an unrelated hepatopathy (Steffan and others 2005). Unacceptable gastrointestinal problems requiring cessation of treatment were rare; in one study this was reported in only two of 266 dogs (Steffan and others 2005).

Conclusions and recommendations

Gastrointestinal reactions are the most common adverse events reported in dogs treated with ciclosporin. These are usually mild, do not require treatment, and rarely require discontinuation of ciclosporin.

Suggestions from the literature to reduce the incidence of vomiting and/or diarrhoea are to start treatment with a low dose (1 to 2 mg/kg every 24 hours) gradually increasing to the therapeutic dose

Table 1: Analysis of 15 trials including 759 dogs treated with ciclosporin for canine atopic dermatitis

	Total	Fontaine and Olivry 2001	Iwasaki and others 2002	Olivry and others 2002a	Olivry and others 2002b	Steffan and others 2003	Olivry and others 2003	Burton and others 2004	Bensignor and Guaguère 2004	Steffan and others 2005	Thelen and others 2006	Carlotti and others 2009	Nuttall and others 2012	Kovalik and others 2011a*	Kovalik and others 2012	Dip and others 2013
Number (%) of dogs	759	14	92	61	15	117	30	41	15	266	25	8	21	13	16	25
Vomiting	26%	2 (14)	10 (11)	23 (38)	1 (7)	43 (37)	6 (20)	4 (10)	5 (33)	82 (31)	0	0	6 (29)	3 (23)	2 (13)	10 (40)
Soft stools/diarrhoea	15%	0	13 (14)	21 (34)	3 (20)	6 (5)	0	4 (10)	0	53 (20)	0	0	2 (10)	2 (15)	5 (31)	5 (20)
Miscellaneous	3%	0	0	0	1 (7)	10 (9)	1 (3)	0	0	0	10 (40)	0	0	0	0	2 (8)
Loss of appetite	2%	0	1 (1)	0	0	5 (4)	0	0	0	8 (3)	0	0	1 (5)	0	0	0
Nodules/cyst	1%	0	0	0	0	7 (6)	0	0	0	3 (1)	0	0	0	0	0	0
Urinary tract infection	1%	0	0	0	0	0	0	0	0	10 (4)	0	0	0	0	0	0
Gingival hyperplasia	1%	0	0	0	0	3 (3)	0	0	0	6 (2)	0	0	0	0	0	0
Lethargy/lameness	1%	0	0	0	1 (7)	0	0	0	1 (7)	6 (2)	0	0	0	0	0	1 (4)
Reproductive	1%	0	0	0	0	7 (6)	0	0	0	0	0	0	0	0	0	0
Papillomatosis	1%	0	0	0	1 (7)	0	1 (3)	0	0	4 (2)	0	0	0	0	0	1 (4)
Lymphadenopathy	0.8%	0	0	0	0	0	0	0	0	6 (2)	0	0	0	0	0	0
Neurological	0.8%	0	0	0	0	0	0	0	0	4 (2)	1 (4)	0	0	0	0	1 (4)
Other urine abnormalities	0.3%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (8)
Urticaria/ angio-oedema	0.3%	0	0	0	1 (7)	0	1 (3)	0	0	0	0	0	0	0	0	0
ADR requiring cessation of therapy	5%	0	5 (5)	0	2 (13)	10 (9)	5 (17)	0	0	11 (4)	3 (12)	0	0	0	0	0
Total	59.2%	14%	31%	72%	68%	79%	46%	20%	40%	73%	56%	0%	44%	38%	44%	88%

* All the trials used 5 mg/kg ciclosporin as Atopica (Novartis Animal Health) except Kovalik and others 2011a, which used 5 mg/kg ciclosporin as Equoral oral solution (Teva Pharmaceuticals)
ADR Adverse drug reaction

(5 mg/kg every 24 hours) or reducing the dose regime (eg, from daily to every other day or twice weekly). Other options include chilling or freezing the ciclosporin for 30 to 60 minutes before administration (Palmeiro 2013). Administering ciclosporin in food may also help (Palmeiro 2013), although adverse effects were equally frequent with and without food in one small study (Thelen and others 2006). If necessary, vomiting may be managed with antiemetics (eg, maropitant or metoclopramide) (Palmeiro 2013) or gastric protectants (eg, sucralfate, cimetidine or ranitidine). Sucralfate should be given at least one hour before ciclosporin to avoid reducing absorption and bioavailability. High-fibre supplements (such as canned pumpkin) and probiotics may help ameliorate soft stools or diarrhoea (Palmeiro 2013). Zinc-carnosine and vitamin E supplementation (Gastri-Calm; Teva Animal Health) has failed to alleviate gastrointestinal side effects associated with ciclosporin therapy (Wilson and others 2011).

Papillomatous, psoriasiform and/or verrucose dermatitis

Papillomatous skin lesions or other 'skin hyperplasia' were observed in five of 672 (0.7 per cent) dogs in one meta-analysis (Steffan and others 2006). Proliferative skin lesions were seen in 1 per cent of the 759 dogs in Table 1. Three cases of psoriasiform lichenoid dermatitis were also described (Werner 2003). These responded to withdrawal of ciclosporin and treatment with antibiotics. Papillomatosis and verrucose dermatitis have also been reported to resolve following reduction of the dose or withdrawal of treatment (Seibel and others 1989a, Olivry and others 2002b, Favrot and others 2005). The incidence and severity appears to be dose related, with generalised papillomatosis seen in five of eight dogs given 45 mg/kg daily for 12 months (Donatsch and Ryffel 1986).

These lesions are rarely associated with papillomavirus infection (Donatsch and Ryffel 1986, Seibel and others 1989a, Favrot and others 2005). In one study, seven of nine dogs with lesions consistent with psoriasiform lichenoid dermatosis were negative for papillomavirus by immunohistochemistry and PCR (Favrot and others 2005). Histopathological evidence of staphylococci supports the suggestion that these lesions, at least in part, represent a reaction to bacterial colonisation and/or infection (Werner 2003). The other two dogs in the study had verrucose lesions with histopathological evidence of viral infection, including koilocytes and nuclear viral inclusions. These lesions were positive for papillomavirus and PCR amplified DNA characteristic of canine oral papillomavirus and canine papillomavirus type 2. All the lesions resolved on withdrawal of ciclosporin without further treatment. One case of oral viral papilloma was reported in an atopic dog (Radowicz and Power 2005); the papilloma was successfully excised and did not recur despite ongoing ciclosporin treatment.

Conclusions and recommendations

Various hyperplastic lesions of the skin have been associated with ciclosporin treatment in dogs. These are uncommon and rarely of any clinical significance; this assessment is also consistent with reported PV data. Most resolve on dose reduction or cessation of therapy without the need for further treatment.

Gingival hyperplasia

The prevalence of gingival hyperplasia was 1 per cent identified in this review (Table 1), 1.7 per cent in one unpublished meta-analysis of 609 dogs (C. Favrot, unpublished observations) and 1.3 per cent in another analysis of 672 dogs (Steffan and others 2006). In most cases the gingival hyperplasia was mild and did not warrant cessation of therapy. The hyperplasia was probably associated with transforming growth factor beta (TGFβ)-mediated proliferation of the extracellular matrix (Stabellini and others 2002). The effect appears to be dose-dependent although there was individual variation, which may reflect variable metabolism and pharmacodynamics (Seibel and others 1989b). Gingival hyperplasia was particularly severe and frequent in a group of dogs treated with 45 mg/kg daily for 12 months (Donatsch and Ryffel 1986). In an experimental transplantation study, three of four dogs treated with adjusted doses of ciclosporin to maintain whole blood trough concentrations of 400 to 700 ng/ml started to develop moderate to severe gingival hyperplasia by 20 weeks. However, these dogs were also treated with azathioprine and, for the first three months, prednisolone to prevent graft rejection (Nam and others 2008).

Conclusions and recommendations

Gingival hyperplasia is rare with standard doses of ciclosporin used to treat canine AD. In most cases the gingival hyperplasia is mild and of little clinical significance, but in rare cases it can be more severe with significant tooth occlusion and gingivitis. The gingival hyperplasia responds favourably to reduction of the dose or cessation of treatment. Mild cases may require dental hygiene to help prevent gingivitis.

Azithromycin seems to be of additional benefit in humans (Ramalho and others 2007). In one study of 36 dogs with ciclosporin-associated gingival hyperplasia, brushing with an 8.5 per cent azithromycin toothpaste or systemic azithromycin (10 mg/kg) every 24 hours significantly decreased the gingival sulcus depth compared to placebo groups, but there was no change in tooth length or subjective global scores and only one dog in the systemic azithromycin group had complete remission (Rosenberg and others 2013).

Hirsutism or hypertrichosis

Hirsutism or hypertrichosis are rarely reported as adverse effects; less than 1 per cent in one unpublished meta-analysis of 609 dogs (C. Favrot, unpublished observations), with no reports in many studies (Table 1) (Steffan and others 2006). Nevertheless, hirsutism and/or hypertrichosis is frequently reported in dogs treated with ciclosporin (Seibel and others 1989a, Robson and Burton 2003). Initially, some animals experience a heavy shedding approximately four to six weeks after initiation of ciclosporin therapy. Ciclosporin induces the hair follicle to stay in a prolonged anagen (growth) phase and induces catagen (transitional) and telogen (resting) follicles to enter the anagen phase. This causes a somewhat synchronised telogen phase resulting in an increase in shedding. The hair follicles then begin to produce new growth, probably associated with ciclosporin-induced inhibition of the calcineurin-NFAT1 pathway in follicular keratinocytes resulting in the growth of a thicker and glossier haircoat (Gafter-Gvili and others 2003).

Conclusions and recommendations

Hirsutism or hypertrichosis is a benign consequence of ciclosporin therapy. It is rarely clinically significant, but individual dogs may need more frequent grooming to prevent matting of the coat, particularly in interdigital areas.

Infections

Long-term use of immunomodulating agents could increase the risk of infection with bacterial, fungal, viral, protozoal or other organisms such as *Demodex* species. Ciclosporin shows dose and time-dependent immunosuppressive activity, with suppression of interleukin (IL)-2, IL-4, interferon (IFN)-γ, CD25 and CD95 expression by activated T cells (Fellman and others 2011), although in healthy dogs only the effects on IL-2 and IFN-γ were significant (Archer and others 2011). However, one study using 5 mg/kg generic ciclosporin (Equoral) daily for 42 days in 13 dogs did not show any significant effects on metabolic or functional activity of phagocytic cells compared to 1 mg/kg prednisolone (Kovalik and others 2011a). A further in vitro study using the canine keratinocyte cell line CPEK showed that ciclosporin increased IL-8 and tumour necrosis factor-α mRNA expression in response to toll-like receptor 2 ligands (Hendricks and others 2012), suggesting that ciclosporin may actually enhance innate immunity in the skin.

Staphylococcal and *Malassezia* skin and ear infections

Staphylococcal and *Malassezia* skin and ear infections are common in canine AD. However, while these may contribute to on-going inflammation, it is thought that colonisation and infection is a consequence of altered skin barrier function and cutaneous immunity inherent with canine AD (Nuttall and Halliwell 2001, Bexley and others 2013). In one study, treatment with ciclosporin significantly decreased the prevalence of secondary infections (Steffan and others 2003), suggesting that effective control of canine AD reduces the frequency and severity of infections. Psoriasiform lichenoid dermatosis (see above) has been associated with staphylococci, and may be an unusual reaction to bacterial colonisation and/or infection in some dogs on ciclosporin therapy (Werner 2003, Favrot and others 2005). These lesions usually resolve on withdrawal of ciclosporin, but some dogs may also need antibiotic treatment.

Urinary tract infections

Reports of bacteriuria and lower urinary tract infections seem to be rare, reported in just 1.3 per cent of 759 treated dogs (Table 1). In an exception to this, one clinical trial recorded bacteria present in at least one urine sample from 51 per cent of 89 treated dogs (Steffan and others 2005). Only one dog developed clinical evidence of cystitis, although another nine dogs were considered to have asymptomatic urinary tract infections. This has not been reported elsewhere, but urine samples were not routinely examined in all studies (Steffan and others 2006). However, 24 per cent of dogs in this study were positive for bacteriuria at enrolment and the prevalence remained stable throughout the trial, with some fluctuations from positive to negative and vice versa. It is possible that this high prevalence reflected prior therapy with systemic glucocorticoids rather than ciclosporin treatment during the trial.

In a study following 38 dogs for up to two years of treatment, three dogs developed bacteriuria, which was confirmed by culture (Radowicz and Power 2005). A further 18 cultures from random samples with normal sediment exams were negative, and none of the dogs developed clinical signs consistent with a urinary tract infection. A more recent retrospective study reported that 26 of 87 dogs with chronic inflammatory skin disease treated with ciclosporin with and without glucocorticoids for at least five months had at least one positive urine culture (Peterson and others 2012). This was significantly higher than in a non-treated control group, but there were no significant differences between the control group and either dogs treated with ciclosporin alone or ciclosporin and glucocorticoids. No clinical signs of urinary tract infection were noted in any of the dogs. Urine culture was more sensitive than sediment examination, and it is therefore possible that earlier studies have underestimated the prevalence of bacteriuria. However, it is difficult to differentiate the effect of the glucocorticoids from that of the ciclosporin in this study.

Other infections

Other bacterial infections (including gingivitis, pyometra and respiratory tract infections) have been seen in dogs treated with ciclosporin, but these are uncommon and no more frequent than in the general canine population (Steffan and others 2006). Clostridial enteritis was diagnosed in one of 266 dogs in one trial (Steffan and others 2005), while a further dog developed a non-specific metronidazole responsive diarrhoea. Disseminated nocardiosis was seen in one dog treated with ciclosporin and ketoconazole for AD (Paul and others 2010).

Other infections are rare. One dog on a renal transplant dose of ciclosporin developed toxoplasmosis, although the dog was also treated with prednisolone and azathioprine to prevent transplant rejection (Bernsteen and others 1999). This case was associated with a seropositive donor and possible reactivation of latent *Toxoplasma* cysts in the renal allograft. There is a single case report of reactivation of leishmaniasis in a four-year-old chow chow dog treated with 5 mg/kg ciclosporin daily for presumed AD. The dog had been successfully treated a year earlier with meglumine antimonate and allopurinol, and responded to the withdrawal of ciclosporin, and additional treatment with meglumine antimonate and allopurinol (Navarro and others 2008). Another study reported that treatment with 3.5 mg/kg ciclosporin and glucantime for six days in dogs with leishmaniasis was well tolerated with no evidence of clinical relapse (Pugliese and others 1997).

Viral, fungal and *Neospora* infections were also seen in dogs treated with ciclosporin, prednisolone or methylprednisolone, and azathioprine or chlorambucil to manage immune-mediated disease. Multiple papillomavirus-associated epidermal hamartomas and squamous cell carcinomas in situ were seen in a dog following chronic treatment with prednisolone and ciclosporin (Callan and others 2005). Despite this, concurrent therapy with ciclosporin (5 mg/kg every 24 hours) and prednisolone (1 mg/kg every 24 hours for seven days and then 1 mg/kg every 48 hours for 14 days) did not significantly increase the incidence of adverse effects compared to using ciclosporin alone. Adverse effects were restricted to those expected from ciclosporin (ie,

Table 2: Top 10 adverse clinical signs associated with ciclosporin treatment in dogs reported to pharmacovigilance between September 2002 and March 2012

Adverse clinical signs	Absolute incidence*
All suspected adverse events	71.81
Vomiting	27.57
Diarrhoea	13.46
Lethargy	9.58
Abnormal test result†	8.59
Pruritus	7.80
Anorexia	6.65
Hyperactivity	3.22
Gingival disorder	2.98
Tachypnoea	2.96
Polydipsia	2.58

* Number of dogs affected/1 million capsules sold
† Includes various clinical pathology values outside of their normal range

mild to moderate gastrointestinal upsets) and prednisolone (ie, polyphagia, polyuria/polydipsia and other systemic effects); none were severe enough to warrant cessation of therapy and no infections were noted (Dip and others 2013).

Conclusions and recommendations

It is likely that effective management of canine AD will reduce the frequency of secondary staphylococcal and *Malassezia* skin and ear infections. The presence of such infections is not, therefore, a contraindication for treatment with ciclosporin. Topical and/or systemic antimicrobial therapy should nevertheless be used to manage infections in appropriate cases (Beco and others 2013).

Other opportunistic infections are rare. Routine urinalysis is not generally indicated in dogs undergoing long-term treatment with ciclosporin at 5 mg/kg, although further studies are required. As a lower urinary tract infection (ie, bacterial cystitis) may (albeit rarely) develop into a potentially life-threatening pyelonephritis in an immunosuppressed dog, periodic urine culture may be prudent. Likewise, in the absence of firm data serological monitoring of leishmaniasis may be warranted for dogs that live in endemic areas. Concurrent treatment with prednisolone for the first three weeks of ciclosporin therapy does not appear to be a concern. Nevertheless, care should be taken in dogs treated at higher doses and/or with long-term concurrent treatment with other immunomodulating or immunosuppressive drugs.

Effects on systemic metabolism and homeostasis

Calcium metabolism

In people, ciclosporin therapy in organ transplant medicine is associated with osteoporosis, osteomalacia and an increased risk of bone fracture (Epstein 1996). This appears to be associated with increased plasma parathyroid hormone (PTH) and decreased 1,25-dihydroxyvitamin D (1,25[OH]2D) concentrations. Despite this, there are no published descriptions of altered bone density or an increased risk of fractures in atopic dogs. In one study, 16 atopic dogs treated with 4.4-6.0 mg/kg ciclosporin every 24 hours for six weeks showed no significant changes in serum concentrations of plasma total and ionised calcium, phosphate, creatinine, 25(OH)D, 1,25(OH)2D, or urinary fractional excretion of calcium and phosphate (Kovalik and others 2012). Mean plasma PTH concentrations significantly increased following ciclosporin treatment, but the proportion of dogs with plasma PTH levels above the reference range was similar before and after treatment. Plasma PTH levels increased in 10 of 16 dogs, but decreased or did not change in the other six dogs, and levels increased out of the reference range in only three dogs. However, the lack of a control group makes it difficult to interpret the significance of these findings.

Glucose metabolism

Diabetes mellitus is rare in dogs treated with ciclosporin. It has been associated with West Highland white terriers in Europe (which is now listed on the European Medicines Agency Summary of Product Characteristics), but overall appears to be no more frequent than in the general canine population (Steffan and others 2006). One dog developed glycosaemia and overt diabetes mellitus three months after completing four months of treatment at 5 mg/kg daily tapered to every other day (Steffan and others 2003). PV data supports the observation that diabetes mellitus is rare; however, it is interesting to note that the PV data also shows that treatment with ciclosporin in West Highland white terriers in the UK appears to be associated with an increased incidence of diabetes mellitus (Roberts and others 2012a). Ciclosporin can increase peripheral insulin resistance and decrease insulin secretion (Wahlstrom and others 1990). These changes are reversible and dogs given 20 mg/kg ciclosporin daily remained normoglycaemic (Basadonna and others 1988). However, a study of 16 dogs with AD showed that treatment with 5 mg/kg ciclosporin once daily for six weeks significantly elevated median serum fructosamine concentrations compared to baseline (Kovalik and others 2011b). Plasma glucose levels were significantly increased and serum insulin concentrations were significantly lower. Peak glucose concentrations were significantly increased following glucagon stimulation tests, but there was no difference in insulin concentrations. No dogs developed overt diabetes mellitus and fructosamine levels remained within the normal reference range in all cases. Interestingly, diabetic dogs show significantly increased total body clearance of ciclosporin compared to healthy dogs, possibly associated with a decreased half-life (9.3 hours compared to 22.6 hours) (Alkharfy 2009).

Miscellaneous

No consistent abnormalities in haematology or serum biochemistry have been associated with ciclosporin therapy in the absence of a concurrent condition (Steffan and others 2003, 2006). In one trial using 3.3 to 6.6 mg/kg, mean haematology and serum biochemistry parameters remained within normal limits after eight and 16 weeks of treatment (Steffan and others 2005). Statistically significant changes were seen in a small number of dogs (including increased red cell, white cell and lymphocyte counts; and changes in urea, creatinine and total protein), but these typically remained within 5 per cent of the baseline values. Other changes included mild hypercholesteraemia in 2.6 per cent of dogs, mild hypocalcaemia in 2.3 per cent, and a 5 to 10 per cent reduction in alanine aminotransferase (ALT) and alkaline phosphatase (AP) activity. Even in dogs given 45 mg/kg ciclosporin daily for 12 months there was no evidence of toxic effects on the liver, kidney, bone marrow or other organs (Donatsch and Ryffel 1986). Mild anaemia and hypoalbuminaemia in two of eight dogs was attributed to malnutrition; mild eosinopenia in three of eight dogs was associated with stress; and increases in β- and γ-globulins were associated with pre-existing infection. All the changes appeared to be reversible. In addition, reversible increased erythrocyte sedimentation rate, hyperproteinaemia, hyperglobulinaemia, hypoalbuminaemia, hypocalcaemia, hypophosphataemia and hypomagnesaemia have also been observed at three and five times the recommended 5 mg/kg dose in healthy beagles (Novartis Animal Health, internal data).

Conclusions and recommendations

Ciclosporin treatment in dogs can result in elevated PTH levels, decreased insulin secretion and peripheral insulin resistance. However, the impact of ciclosporin treatment at the recommended dose on calcium and glucose metabolism is minimal, and there is little evidence of systemic toxicity. Further action or monitoring is not required in most dogs, although periodic monitoring of blood glucose or fructosamine concentrations may detect early signs of reduced insulin production and insulin-resistance. Care should be taken when treating dogs with pre-existing diabetes mellitus or PTH abnormalities.

Neoplasia

It is possible that ciclosporin may inhibit cytotoxic T cell-mediated anti-tumour immune surveillance. In human transplant patients there is a two-fold increase in malignancies following ciclosporin (at up to 18 mg/kg) (Cockburn 1989). Similar findings have been reported in cats (Schmiedt and others 2009) and there is a single case report of lymphoma developing in an 11-year-old German shepherd dog

after four weeks treatment with ciclosporin for anal furunculosis (Blackwood and others 2004). However, the risk appears to be associated with the degree of immunosuppression and not ciclosporin specifically; for example, human transplant patients medicated with azathioprine with or without steroids have a two- to four-fold increased risk of malignancy, but there is no increased risk in patients treated with ciclosporin at 1.3 to 10 mg/kg daily to manage rheumatoid arthritis (Cockburn 1989, van den Borne and others 1998). In addition, there is evidence that ciclosporin may be protective against some forms of colorectal cancer, glioblastoma, bladder tumours and leukaemia through activation of p53 (Weischer and others 2007). In contrast, however, ciclosporin-associated T cell inactivation could suppress antitumour immunity; alterations in TGFβ, IL-6 and vascular endothelial growth factor synthesis in tumour cells could increase growth, metastasis and angiogenesis; and inhibition of DNA repair could facilitate accumulation of mutations.

In a study following 38 dogs for up to two years of treatment, four dogs developed tumours (two malignant mammary tumours [seven- and four-year-old dogs], one mast cell tumour [10-year-old dog] and one splenic haemangiosarcoma [13-year-old dog]) (Radowicz and Power 2005). Treatment was discontinued in two dogs and maintained in two dogs, and all four had a good outcome following surgical removal of the tumours. One further dog was euthanased for an osteosarcoma that arose 22 months after discontinuation of ciclosporin treatment. Two tumours (a benign fibroma and a benign basiloma) were seen in a group of eight healthy dogs given 45 mg/kg daily for 12 months (Donatsch and Ryffel 1986). In one clinical trial, histiocytomas developed in three of 266 dogs (Steffan and others 2005); one was surgically removed and two spontaneously regressed without recurrence.

Despite this, there has been no increased prevalence of neoplasia reported in any published clinical trials. A single centre, retrospective study of 51 dogs receiving ciclosporin from six to 30 months did not reveal an increased incidence of neoplasia compared to the general dog population (Radowicz and Power 2005). Moreover, a retrospective case control study did not find that ciclosporin treatment for canine AD was a significant risk factor for cutaneous lymphoma (Santoro and others 2007). Pharmacovigilance data from 2009 to 2012 showed that 160 neoplasms were suspected in ciclosporin-treated dogs, primarily lymphoma/lymphosarcoma, one of the most common neoplasms of dogs. The incidence of neoplasia in ciclosporin-treated dogs was similar to that of the general population (Dobson and others 2002).

Approximately 1 per cent of treated dogs developed a benign lymphadenomegaly (Steffan and others 2006; Novartis Animal Heath, unpublished observations). This was self-limiting and reversible, and was not associated with malignant transformation. The cause was unknown, but did not appear to involve infection or inflammation.

Conclusions and recommendations

Ciclosporin therapy is not a risk factor for neoplasia at standard doses used to manage canine AD. However, because of the potential impact on tumour growth and development, ciclosporin is contraindicated in the presence of neoplasia as ciclosporin may affect the expression of undiagnosed neoplastic conditions.

Renal failure

In people, renal failure is a frequent severe adverse effect. Acute nephrotoxicity is rare with short-term treatment, but dose-dependent and reversible elevations in urea and creatinine associated with decreased glomerular filtration are common (Faerber and others 2001). Vasoconstriction of the afferent artery results from endothelin and thromboxane release and activation of the renin-angiotensin-aldosterone system (RAAS). Long-term treatment can result in dose-dependent irreversible renal damage, renal failure and hypertension (Markham and others 2002).

Renal failure associated with ciclosporin treatment in canine AD has not been reported in any clinical trials or other publications. There are individual cases of increased urea and/or creatinine levels above reference ranges, but these were either associated with pre-existing renal disease or were variable and inconsistent with time. In one unpublished study (H. Power, unpublished observations), 15 of 266 dogs had elevated creatinine levels after eight or 16 weeks of treatment, but only eight of 265 dogs had elevated creatinine at both eight and 16 weeks. In the same trial, proteinuria was reported in 43 of 154 dogs from at least one time point. The frequency of proteinuria did not increase during the study, with 23 dogs positive at enrolment but negative during the trial and 25 dogs negative at enrolment but positive during the trial. None of the dogs developed clinical signs consistent with renal failure and intervention was unnecessary. In another study where 38 dogs had regular blood samples analysed every six months for up to two years of treatment there were no consistent abnormalities in haematology or biochemistry parameters associated with ciclosporin (Radowicz and Power 2005). Most abnormalities were associated with concurrent conditions. Two dogs had consistently elevated alkaline phosphatase levels, but remained healthy.

Dose dependent increases in renal arterial resistance have been reported in experimental dog models (Donatsch and Ryffel 1986, Carrier and others 1991). However, nephrotoxicity, renal failure and hypertension have not been reported in dogs that received up to 14 mg/kg daily for up to six months or 45 mg/kg ciclosporin daily for up to 12 months (Donatsch and Ryffel 1986, Vaden and others 1995). Long-term administration of 20 mg/kg ciclosporin daily did activate the RAAS, resulting in chronic sodium retention but not hypertension in one experimental canine model (Ciresi and others 1992). It is possible that the canine RAAS is less responsive to ciclosporin than in human or laboratory models.

Conclusions and recommendations

Ciclosporin-associated nephrotoxicity, renal failure and hypertension seems to be species specific and has not been recognised in dogs. Routine monitoring of renal function is not necessary, but care should be taken with dogs that have pre-existing or concurrent renal disease.

Neurological adverse effects

Some 10 to 28 per cent of people treated with ciclosporin experience a variety of neurological problems, including seizures, paraesthesia, cramps, weakness, ataxia, blindness, psychoses and hallucinations. Most are mild, but severe neurotoxicity is seen in 5 per cent of patients (Bechstein 2000). Neurotoxicity in humans is dose dependent and is associated with transplant patients, liver failure, hypertension, elevated cholesterol, decreased magnesium and concurrent glucocorticoid therapy (Bechstein 2000). This may result from decreased perfusion and ischaemia of the white matter. Acute mild neurotoxicity is usually reversible but chronic and/or more severe damage may be permanent.

Neurotoxicity is rare in dogs, with only 0.8 per cent of 759 treated dogs reported to have a neurologic problem (Table 1). Neurological problems were reported at a prevalence of 1 to 4 per cent in two clinical trials (Steffan and others 2005, Thelen and others 2006), but were not observed in most trials and have a prevalence of less than 1 per cent in meta-analyses (Steffan and others 2006). Seizures were uncommon and no more prevalent than in the general population (Kearsley-Fleet and others 2013). In most cases seizures were associated with underling conditions such as brain tumours and idiopathic epilepsy (Steffan and others 2005).

Conclusions and recommendations

Neurological complications are rare and not expected with ciclosporin use.

Other adverse effects

Lethargy and/or weakness were observed in 1 per cent of 759 treated dogs (Table 1) and up to 2.2 per cent of dogs in another meta-analysis (Steffan and others 2006). Pruritus, urticaria, angio-oedema, swollen pinnae and cutaneous flushing have been occasionally noted after administration of Atopica (Olivry and others 2002b, Thelen and others 2006, Novartis Animal Health, unpublished data). This may represent an idiosyncratic immune-mediated drug reaction to ciclosporin and/or the excipients in the formulation. Clinical signs appeared rapidly and completely resolved after withdrawal of the medication. Preliminary studies in three dogs suggested that ciclosporin may increase platelet procoagulant activity (Thomason and others 2012),

but no clinically significant effects on coagulation have been reported. A variety of other adverse effects, including sebaceous adenitis, crusty dermatitis, excessive shedding, coarse coat, alopecia, (pyo)granulomatous nodules, cutaneous cysts, shaking/trembling, hindlimb twitching, panting, depression, irritability, hyperactivity, increased light sensitivity and reluctance to go outside have been reported in clinical trials and other studies (Steffan and others 2006, Novartis Animal Health, unpublished data). However, these affected less than 2 per cent of treated dogs, and no clear causal relationship with ciclosporin administration could be established. In one unpublished meta-analysis, musculoskeletal problems including joint pain and lameness were seen in eight of 609 (1.3 per cent) dogs treated with ciclosporin (C. Favrot, unpublished observations).

Vaccination

Ciclosporin may interfere with vaccination efficacy and there is a potential for adverse effects from attenuated organisms in immunosuppressed animals. In adult cats treated with 24 mg/kg/day of ciclosporin (>3X the therapeutic dose), vaccine titre levels were adequate for protection following booster vaccination. In contrast, treated cats failed to mount a humoral response to a novel vaccination (FIV). However, there are no specific data on lack of efficacy and/or adverse effects associated with treatment at standard doses in adult dogs that have received a primary course of vaccination. In a small study, 16 dogs that received either 20 mg/kg daily of ciclosporin or placebo for 56 days were vaccinated on day 27 with killed rabies and a multivalent (distemper, hepatitis, leptospirosis, parainfluenza and modified live parvovirus) vaccine. None of the dogs, including the placebo-treated controls, showed an adequate antibody titre response to the multivalent vaccine, whereas all the dogs in both groups responded to the killed rabies vaccine. Nevertheless, the current Summary of Product Characteristics (revised February 2013) recommends that animals should not be given a live or inactivated vaccine during treatment or within a two-week interval before or after treatment.

Conclusions and recommendations

From a public health standpoint, and in accordance with USA legal requirements, killed vaccines (such as the rabies vaccine) produced good antibody titres and treatment with ciclosporin is not considered a contraindication for vaccination. The decision whether or not to vaccinate a dog during treatment must be based on a cost-benefit analysis, including the consequences of relapse, the feasibility of using alternative treatments to cover the treatment gap before and after vaccination, and the necessity for vaccination taking into account likely exposure and risk. Serum antibody titres can be used to help determine the need for booster vaccination.

Reproduction

Doses of 30 to 100 mg/kg in laboratory animals are embryo- and fetotoxic, although no effect was seen at doses of 17 to 30 mg/kg. Safety has not been studied in or reported in breeding males and breeding, pregnant or lactating females at standard doses. However, ciclosporin passes the placenta barrier and is excreted via milk, leading to potential exposure of the fetus and neonates. Non-specific effects on reproductive behaviour were reported in seven of 117 dogs in one clinical trial in dogs (Steffan and others 2003), although this has not been noted in other clinical trials where breeding, pregnant or lactating animals were excluded (Table 1).

Conclusions and recommendations

In the absence of specific safety studies, ciclosporin is not for use in animals intended for breeding, or those that are pregnant or lactating.

Metabolism and drug interactions

Ciclosporin is mainly metabolised through the liver and, to a lesser extent, in the intestine, particularly by cytochrome P450 (CYP3A4). Metabolism involves hydroxylation and demethylation to inactive metabolites that are mainly excreted in faeces (<10 per cent in urine). Ciclosporin is also a p-glycoprotein substrate. Substances that affect cytochrome P450 and/or p-glycoprotein could therefore alter ciclosporin metabolism. However, the extent of the drug interaction shows individual variation, probably associated with variable cytochrome P450 and/or p-glycoprotein distribution and activity, as well as factors such as age and concurrent conditions (Dresser and others 2000, Robson 2003).

Competitive inhibitors of cytochrome P450 activity may extend the half-life of ciclosporin, increasing ciclosporin concentrations in plasma. Ketoconazole administered at 5 to 10 mg/kg can increase the blood concentration of ciclosporin in dogs up to five-fold. This increase is clinically relevant and ketoconazole has been used to reduce the dose of ciclosporin by 38 to 90 per cent (Campana and others 1996, Dahlinger and others 1998, Mouatt 2002, Guaguère and others 2004, O'Neill and others 2004, Palmeiro 2013). However, the interaction can be highly individual, with a 10 to 40 per cent variation in tough ciclosporin levels. It can also take two to four weeks to stabilise plasma levels after dose adjustment (Mouatt 2002, Robson 2003).

Ciclosporin plasma levels are not predictive of clinical efficacy in dogs or cats with AD (Guaguère and others 2004, Palmeiro 2013), and are not predictive of safety for cats (Roberts and others 2012b), as plasma concentrations were highly variable. If concomitant treatment is necessary, dogs should be carefully monitored and it is recommended that the initial dose should be halved or the dose interval doubled (Palmeiro 2013). The most recent study concluded that peak plasma, trough plasma and skin concentrations of ciclosporin in six healthy beagles were similar after treatment with 5 mg/kg ciclosporin alone or 2.5 mg/kg ciclosporin combined with 2.5 mg/kg ketoconazole (Gray and others 2013). In all studies the effect was variable between individual dogs and further individual dose adjustments may be required. Fluconazole also significantly increases ciclosporin availability in dogs, requiring dose reductions of ciclosporin of 29 per cent to 51 per cent (Katayama and others 2008). However, as itraconazole is more specific for fungal cytochromes it has less activity on cytochrome P450 and ciclosporin metabolism. Effects are variable, but itraconazole may increase plasma concentrations two-fold (Campana and others 1996, Dahlinger and others 1998, O'Neill and others 2004). Concomitant treatment with these azole drugs is generally well tolerated, but enhanced nephrotoxicity, gingival hyperplasia and insulin resistance were reported in people (Campana and others 1996). Long-term safety of these combinations has not been established.

Erythromycin may increase ciclosporin plasma levels up to two-fold (Campana and others 1996). There are anecdotal reports of decreased ciclosporin concentrations following treatment with clindamycin, but a study in six dogs showed no effect and there is no evidence of any clinically significant interaction (Campana and others 1996, Guaguère and others 2004).

Data from humans suggests that metoclopramide decreases clearance and increases the half-life of ciclosporin, effectively increasing availability by 30 per cent (Campana and others 1996), but this has not been seen in dogs (Radwanski and others 2011). Cimetidine and ranitidine may also increase ciclosporin availability (Campana and others 1996), although cimetidine did not have any clinical significant interaction with ultramicronised emulsified ciclosporin (Atopica) in dogs (Guaguère and others 2004). Cimetidine appeared to delay absorption of ciclosporin, but did not affect maximal concentration or volume of distribution (Daigle and others 2001).

The calcium channel blocker diltiazem also increases plasma levels of ciclosporin (Robson 2003). A dose of 1 mg/kg every other day was reported to facilitate long-term control of pruritus and anal furunculosis in two dogs treated with 5 mg/kg ciclosporin every other day (Robson 2003). Diltiazem has also been shown to prevent renal vasoconstriction following ciclosporin administration in dogs (Carrier and others 1991) and to reduce hypertension in people (Lebwohl and others 1998).

Liquid or freeze-dried grapefruit juice increases intestinal absorption of ciclosporin, probably through effects on intestinal mucosa cytochrome P450 and p-glycoprotein activity. In eight healthy dogs, 10 g of powdered whole grapefruit resulted in 29 per cent faster mean time to maximum plasma concentrations (C_{max}), 54 per cent larger area under the curve (AUC) and 38 per cent lower clearance, although 2 g had no effect (Radwanski and others 2011). In another study in two healthy crossbred dogs, grapefruit juice doubled the C_{max} and increased AUC values of ciclosporin by 25 to 27 per cent, although

there was little change in the time to C_{max} or half-life (Amatori and others 2004).

Drugs that enhance cytochrome P450 and p-glycoprotein activity, such as phenobarbital and trimethoprim-sulfonamides may lower the plasma concentration of ciclosporin (Campana and others 1996). Similarly, St John's Wort significantly decreases C_{max} and AUC, and increases the apparent volume of distribution and clearance in dogs (Fukunaga and Orito 2012). The effects can last for up to seven days after administration.

Ciclosporin is a substrate and an inhibitor of the MDR1 P-glycoprotein transporter. Therefore, the co-administration of ciclosporin with P-glycoprotein substrates such as macrocyclic lactones (eg, ivermectin and milbemycin) could alter the pharmacokinetics of either molecule, potentially resulting in higher blood levels of the drugs. In theory, this could decrease the efflux of such drugs from blood-brain barrier cells, potentially increasing the risk of CNS toxicity. Ciclosporin may also increase the risk of nephrotoxicity with aminoglycosides and trimethoprim (Campana and others 1996). There is speculation that ACE inhibitors may also increase nephrotoxicity in humans (Campana and others 1996), but there is no evidence for this in dogs (Guaguère and others 2004).

Ciclosporin is highly bound to plasma proteins and lipoproteins. However, clinically significant alterations in metabolism through displacement by protein-binding drugs and/or changes in lipoprotein levels have not been reported in dogs (Campana and others 1996).

The interaction between glucocorticoids and ciclosporin is complex and unclear. Variable results, including no changes, increased clearance and decreased plasma levels, and decreased clearance with increased plasma levels have been seen in humans and animal models with concomitant treatment (Campana and others 1996). However, no pharmacokinetic interaction between methyl-prednisolone (1 mg/kg) and ciclosporin (20 mg/kg) was seen in dogs (Guaguère and others 2004). Nevertheless, while short-term two to three week concurrent treatment with glucocorticoids and ciclosporin appears well tolerated (Dip and others 2013), long-term concomitant therapy should be avoided unless clinically justified and treated animals should be monitored carefully for signs of immunosuppression.

Conclusions and recommendations

Ciclosporin is well tolerated and concomitant treatment with a wide range of drugs (including penicillins, cephalosporins, fluoroquinolones and NSAIDs) is safe (Campana and others 1996, Guaguère and others 2004). However, there are certain specific interactions particularly involving cytochrome P450 and the MDR1 P-glycoprotein transporter. Short-term concomitant treatment with drugs that affect these pathways resulting in transient elevations in plasma ciclosporin concentrations are unlikely to be clinically significant. However, long-term concomitant therapy should be clinically justified, carefully monitored and where necessary, appropriate dose adjustments should be made.

Monitoring ciclosporin levels

There is marked individual variability in ciclosporin pharmacokinetics. In dogs, for example, trough levels can vary from six- (Griffiths and others 1999) to 12-fold (Seibel and others 1989b), and peak concentration can vary from 2.2- (Daigle and others 2001) to 3.4-fold (Steffan and others 2004) following a constant dose. This may be related to individual variation in hepatic cytochrome P-450 3A and intestinal p-glycoprotein activity, although obesity may also be a factor through preferential distribution to adipose tissue and lipoprotein binding. Trough ciclosporin levels correlated with the obesity index in a study of humans with psoriasis (Cather and others 2001).

Monitoring of plasma ciclosporin levels in transplant medicine is used to ensure that treatment effectively prevents rejection with minimal adverse effects. This is justified by the relatively small margin of safety with higher doses, the consequence of failure and the care needed for dose adjustment. However, no correlation between 24 hour plasma trough levels and efficacy or safety in canine AD has been established (Robson 2003, Guaguère and others 2004, Palmeiro 2013). Values for AUC appear to be better correlated with efficacy and safety than 12 or 24 hour tough levels (Robson 2003, Guaguère and others 2004, Palmeiro 2013). In addition, there is poor correlation between peak or trough plasma concentrations and skin concentration, which may be a better predictor of clinical efficacy in canine AD (Gray and others 2013).

Conclusions and recommendations

Monitoring of ciclosporin plasma levels in the treatment of canine AD is not justified. However, monitoring could be warranted where the margin of safety is lower, for example at higher doses or when ciclosporin is combined with a drug known to increase plasma levels (eg, ketoconazole). It may also be worth measuring plasma levels in dogs that have unexpectedly severe adverse effects or treatment failures (Robson 2003, Palmeiro 2013). In these cases, clinicians should use individual laboratory standards when evaluating the results as levels from different high performance liquid chromatography (HPLC) and immunological tests vary markedly (Vaden 1997, Robson 2003, Guaguère and others 2004, Palmeiro 2013).

Conclusions

This review shows that the safety profile for ciclosporin is well characterized. The majority of adverse effects seen in the clinical trials and literature are supported by a decade of PV data and the adverse effects associated with ciclosporin treatment are described in the approved labelling (derived from results of target animal safety, clinical trial, and PV data). Gastrointestinal signs, primarily vomiting and diarrhoea, are the most often related events accounting for about 50 per cent of the adverse effects. Most of the adverse effects occurred with daily dosing and tended to resolve with acclimation, dose reduction, or discontinuation. As with any drug that modifies the immune system, ciclosporin may increase susceptibility to infection and development of neoplasia. Various substances are known to competitively inhibit or induce the enzymes involved in the metabolism of ciclosporin, in particular cytochrome P450. In certain clinically justified cases, an adjustment of the dosage of the veterinary medical product may be required.

Conflict of interests

Tim Nuttall has received consultancy and lecture fees from Novartis Animal Health. Elizabeth Roberts and Doug Reece are employees of Novartis Animal Health.

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