

Papers

Evaluation of a human generic formulation of ciclosporin in the treatment of canine atopic dermatitis with in vitro assessment of the functional capacity of phagocytic cells

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To compare the efficacy, tolerability and safety of a generic formulation of ciclosporin for human beings with prednisone in the treatment of canine atopic dermatitis), human generic ciclosporin A (hgCsA) (5 mg/kg daily) and prednisone (1 mg/kg daily for seven days, followed by 1 mg/kg every second day) were administered to 13 and seven dogs with atopic dermatitis, respectively, for 42 days. Skin changes were assessed using a modified canine atopic dermatitis extent and severity index (mCADESI-01) and a pruritus intensity scale system. The in vitro functional capacity of phagocytic cells was assessed using the tetrazolium reductase activity and zymosan-stimulated tetrazolium reductase activity tests, as well as measurements of the percentage phagocytic activity and the ingestion capacity of phagocytic cells. Haematological and biochemical parameters were also monitored. There was a greater than or equal to 50 per cent reduction from the baseline in mCADESI-01 scores in 84.6 and 100 per cent of dogs, and a greater than or equal to 50 per cent reduction from the baseline in pruritus scores in 76.9 and 85.7 per cent of dogs, treated with hgCsA and prednisone, respectively. No important adverse physical, haematological or biochemical effects occurred with either drug and no statistically significant changes were detected in any of the four tests assessing the functional activity of phagocytes. The generic formulation of ciclosporin was effective in reducing the severity of physical signs of canine atopic dermatitis and was well tolerated.

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IN human beings, ciclosporin A (CsA) was first used to reduce graft rejection but it soon became apparent that it was also effective in the management of severe atopic dermatitis (Zaki and others 1996). The initial formulation was in vegetable oil, available as a drinkable solution or as soft gelatin capsules (Sandimmune; Sandoz-Pharma). Subsequently, a microemulsified preparation (Neoral; Novartis) was designed to improve bioavailability (Zadrazil and others 2004).

The potential efficacy of CsA in the treatment of canine atopic dermatitis was first reported by Fontaine and Olivry (2001). Subsequent studies established that 5 mg/kg microemulsified CsA (Neoral oral solution 100 mg/ml) per day constituted an induction dose that controlled the physical signs of canine atopic dermatitis (Olivry and others 2002). Subsequently, a microemulsified formulation of CsA (Atopica; Novartis Animal Health), equivalent to the human formulation Neoral (Novartis), was licensed for use in dogs, but only in certain countries.

Recently, human generic formulations of CsA (hgCsA) for use in human beings have been developed and some of these are available commercially worldwide (see www.equoral.net/files/regulatory.html). Equoral (Teva Pharmaceuticals) is one such hgCsA microemulsified formulation. Studies comparing the bioequivalence and pharmacokinetic conversion of Neoral with that of Equoral have demonstrated that these drugs are bioequivalent and interchangeable in stable human patients (Andrysek and others 2003, Masri and oth-

ers 2003, 2004). The effects of Equoral in the management of canine atopic dermatitis have not been reported.

The present study was undertaken primarily to evaluate the efficacy and potential for adverse effects of Equoral in the control of canine atopic dermatitis in countries where Atopica is currently not available, and to compare these with the effects of a positive control, prednisone. In addition, its effect on the phagocytic function of canine granulocytes was also evaluated.

Materials and methods

Study design

This trial was designed as a single-investigator, prospective, blinded, pilot study of 42 days' duration. The study protocol was reviewed and approved by the Ethical Committee of Animal Care and Use at the Agricultural University, Lublin, Poland. Owners' informed consent was obtained for inclusion of the dogs in the study.

Twenty dogs were recruited over a 12-month period and allocated to one of two groups (A or B) on day 0 after all inclusion criteria were confirmed. Unbalanced randomisation was carried out such that approximately two of three dogs ($n=13$) were enrolled in group A and seven were enrolled in group B. This was undertaken to increase the number of animals undergoing ciclosporin therapy because the effect of prednisone, the reference treatment, was already well documented.

The dogs in group A received 5 mg/kg hgCsA (Equoral oral solution; Teva Pharmaceuticals) once daily, orally, two hours before or after feeding for 42 days, whereas those in group B received 1 mg/kg prednisone (Encorton; Polfa Pharmaceuticals) once daily, orally, with food for seven days and then 1 mg/kg every second day for 35 days. The principal investigator was blinded to the treatment protocol administered to each dog.

Inclusion criteria

Dogs were considered eligible for inclusion in the study only if they satisfied established criteria for the diagnosis of canine atopic dermatitis (DeBoer and Hillier 2001). Flea and mite infestations were ruled out by standard diagnostic techniques and response to treatment. Cutaneous adverse reactions to food were ruled out by the failure to show any improvement when fed an elimination diet with the exclusion of all other foodstuffs for a minimum of six weeks. Gravid or lactating dogs were not included in the study.

Withdrawal times of medications administered before the study

Drugs that might have influenced the apparent response to hgCsA or prednisone were withdrawn. The withdrawal time for glucocorticoid-containing oral or topical medications was a minimum of three weeks, while for injectable depot glucocorticoids, the withdrawal time was eight weeks. Antihistamines (H_1 receptor antagonists) were withdrawn for at least two weeks. When allergen-specific immunotherapy (ASIT) was discontinued because of the lack of efficacy, the withdrawal time was three months before inclusion. Essential fatty acids and vitamin E were either withdrawn four weeks before the beginning of the study, or these substances were administered throughout the study at unchanged dosages (potent medicines that might have confused interpretation of the results were withdrawn, while less potent medicines with constant modes of action were continued).

Concurrent medications

ASIT was maintained if it had been used for at least 12 months. A topical flea control product, selamectin (Stronghold; Pfizer), was applied to all dogs in both groups monthly throughout the study period. Dogs with superficial bacterial pyoderma or *Malassezia pachydermatis*-associated dermatitis were treated before enrolment. If indicated, relapses of secondary skin infections, for example, bacterial pyoderma or *Malassezia* dermatitis, were treated topically if they occurred during the study. No other medications were administered for the duration of the study.

Exclusion criteria

The owners were free to withdraw their animals from the trial at any point. Exclusion criteria were as follows: non-adherence to the

trial instructions by the owners; exhibition of unacceptable adverse effects by the dog in response to hgCsA or prednisone; the need for medication not in the protocol; or development of a medical or surgical condition requiring treatment that would affect the outcome of the study.

Clinical scoring

mCADESI-01 score

The severity of skin lesions was scored by the principal investigator on day 0 (before administration of the medication) and on days 14, 28 and 42 using a modification of the first canine atopic dermatitis extent and severity index (mCADESI-01 [Olivry and others 2002]), as previously described by Colombo and others (2005). Skin lesions were scored for erythema, hyperpigmentation, lichenification, papular/pustular lesions and greasy seborrhoea at 36 different body sites. The lesions were graded using a scale from 0 to 3 (none, mild, moderate and severe).

Pruritus score

The intensity of pruritus was evaluated at the same time points as the mCADESI-01 using a pruritus intensity scale (PIS) (Laffort-Dassot and others 2004). This system ascribes a variable number of points from 1 to 10, on the basis of a combination of intensity (low, mild, medium or marked) and frequency (sporadic, less frequent, frequent or constant) of pruritus.

Adverse effects

Potential adverse effects of hgCsA and prednisone were monitored by evaluation of the physical signs and standard haematological and biochemical parameters at all time points (days 0, 14, 28 and 42).

Functional capacity of phagocytes

In order to monitor the influence of hgCsA and prednisone on innate cellular immunity (phagocytic activity and oxidative burst), the functional capacity of phagocytic cells in vitro was determined by a series of tests.

The tetrazolium reductase activity of phagocytes was measured by the nitroblue tetrazole (NBT) test. Heparinised blood samples were incubated with buffered NBT 0.1 per cent solution and phosphate buffer 0.15M (pH 7.2) for 15 minutes at 37°C. Subsequently, smears were prepared, stained with 0.1 per cent solution of safranin O staining and examined microscopically to determine the percentage of neutrophils exhibiting intracytoplasmic deposits of NBT-formazan (Park and others 1968, Czygier and others 2007).

The zymosan-stimulated tetrazolium reductase activity of phagocytes was measured using the NBT-stimulated (NBTS) test. Heparinised blood samples were incubated with buffered NBT solution as described previously, with the addition of zymosan A (10 mg/ml), which consists of protein-carbohydrate complexes prepared from yeast cell walls and used to induce experimental sterile inflammation. When evaluating the preparation, only phagocytes that contained at least three zymosan A particles were counted (Park and others 1968).

The percentage phagocytic activity was evaluated using a protocol established by Ladosz (1968) and modified by Kostro (1993). A quantity of 0.1 ml (600,000 bacteria/ml) of a standard strain of *Staphylococcus aureus* 209P culture was diluted with 0.1 ml serum and incubated for 30 minutes at 37°C. Then, 0.1 ml leucocyte-rich supernatant was added and the resultant solution was incubated for 30 minutes at 37°C. After incubation, smears of the solution were made, fixed in methanol and stained in 2 per cent Mason stain. One hundred cells were examined microscopically and the percentage of phagocytosed bacteria was determined.

The ingestion capacity of phagocytic cells (IP) was also determined, as described by Ladosz (1968), by counting the mean number of phagocytosed staphylococci in 100 granulocytes.

Statistical methods

Observations of all parameters were made on days 14 and 28 to allow intention-to-treat analyses to be made in case animals were withdrawn from the study. The data were analysed at the start of the study to determine whether there were any statistical differences between

TABLE 1: Details of 13 dogs enrolled in group A and treated with human generic formulation of ciclosporin A

Number	Breed	Sex	Age (years)	Weight (kg)
1	American Staffordshire bull terrier	F	1.0	27
2	American Staffordshire bull terrier	FN	4.0	29
3	Border collie	M	3.8	25
4	Dalmatian	MN	3.0	25
5	American Staffordshire bull terrier	MN	1.4	10
6	Labrador retriever	F	1.1	30
7	American Staffordshire bull terrier	M	1.3	22
8	Argentinean mastiff	FN	5.0	42
9	American Staffordshire bull terrier	M	1.6	39
10	Doberman pinscher	MN	2.0	38
11	American Staffordshire bull terrier	F	2.2	33
12	Boxer	FN	1.5	28
13	American Staffordshire bull terrier	M	3.0	33
Mean			2.4	29.3

F Female, FN Neutered female, M Male, MN Neutered male

TABLE 2: Details of seven dogs enrolled in group B and treated with prednisone

Dog	Breed	Sex	Age (years)	Weight (kg)
1	American Staffordshire bull terrier	MN	3.8	29
2	American Staffordshire bull terrier	FN	5.0	27
3	Crossbreed	M	2.6	34
4	American Staffordshire bull terrier	M	1.0	30
5	Crossbreed	FN	4.2	30
6	Chinese Shar Pei	MN	1.6	18
7	Chinese Shar Pei	F	2.0	8
Mean			2.9	25.1

F Female, FN Neutered female, M Male, MN Neutered male

the two groups in terms of age and weight (two-sample *t* test for both), the proportion of males and females (Fisher's exact test) and pruritus and mCADESI-01 scores (Mann-Whitney U test for both). Fisher's exact test was also used to test for differences in the proportion of dogs that had a greater than or equal to 25 and 50 per cent reduction in their mCADESI-01 and pruritus scores, respectively, after 42 days. The reduction of pruritus and mCADESI-01 scores was analysed using the Mann-Whitney U test. For each group, the Wilcoxon signed-rank test was used to analyse differences between days 0 and 42 in the mCADESI-01 and PIS scores, the haematological and biochemical data, and the results of the NBT test, NBTS test, percentage phagocytic activity and IP tests. Differences in mCADESI-01 and PIS scores, haematological and biochemical data and results of NBT, NBTS, percentage phagocytic activity and IP tests between the two groups on days 0 and 42 were compared by the Mann-Whitney U test. Statistical significance was set at $P < 0.05$.

Results

All dogs completed the study. Detailed statistical analyses of comparisons on days 14 and 28 are not presented.

Study population characteristics

Twenty dogs were enrolled in the study, 13 of which were assigned to group A (Table 1) and seven to group B (Table 2). Group A comprised 13 purebreeds of seven males and six females, aged between one and five years (mean 2.4 years), with a mean bodyweight of 29.3 kg. Group B comprised five purebreeds and two crossbreeds. Four were male and three were female, and they were aged between one and five years (mean 2.9 years), with a mean bodyweight of 25.1 kg. There were no statistically significant differences between the two groups in the proportion of males ($P = 0.999$), age ($P = 0.459$) or weight ($P = 0.333$) at the start of the study.

mCADESI-01 scores

The results of the mCADESI-01 scores in groups A and B at the four assessment points are shown in Fig 1a. On day 0, there was no significant difference between the mCADESI-01 scores of dogs in groups A and B ($P = 0.451$). Comparison of scores on days 0 and 42 indicated

that there was a significant reduction in mCADESI-01 scores of group A dogs following treatment with hgCsA ($P = 0.002$) and of group B dogs following treatment with prednisone ($P = 0.022$). Ciclosporin treatment reduced mCADESI-01 scores by at least 25 per cent in 12 of 13 dogs (92.3 per cent) and by at least 50 per cent in 11 of them (84.6 per cent). Prednisone reduced mCADESI-01 scores by at least 25 per cent in all seven dogs (100 per cent) and by at least 50 per cent in six (85.7 per cent). There was no significant difference between the two groups in the proportion of dogs with a greater than or equal to 25 per cent reduction in mCADESI-01 score ($P = 0.999$). Comparison of mCADESI-01 scores of dogs in groups A and B on day 42 indicated that there was no significant difference ($P = 0.113$) in the reduction seen between dogs treated with hgCsA and those treated with prednisone.

Pruritus scores of groups A and B

The results of the pruritus scores in groups A and B at the four assessment points are shown in Fig 1b. On day 0, there was no significant difference between the pruritus scores of dogs in groups A and B ($P = 0.113$). Comparison of scores on days 0 and 42 indicated that there was a significant reduction in the PIS of group A ($P = 0.002$) and group B ($P = 0.022$) dogs. Treatment with ciclosporin reduced pruritus by at least 25 per cent in 11 of the 13 dogs (84.6 per cent) and by at least 50 per cent in 10 of them (76.9 per cent). Treatment with prednisone reduced pruritus by at least 25 per cent in seven dogs (100 per cent) and by at least 50 per cent in six (85.7 per cent). There was no significant difference between the two groups in the proportion of dogs with a greater than or equal to 25 per cent reduction in PIS score ($P = 0.523$) or in the percentage reduction in PIS scores ($P = 0.219$) on day 42.

Influence of hgCsA and prednisone on innate immunity

Test of metabolic activity (NBT test) score

The results of the NBT tests in groups A and B at the four sample points are shown in Fig 1c. There were no significant differences between groups A and B in the NBT test scores on day 0 ($P = 0.113$) or on day 42 ($P = 0.331$). There were also no significant differences in the NBT test scores of group A ($P = 0.239$) or group B ($P = 0.866$) dogs between days 0 and 42.

Test of stimulated metabolic activity (NBTS test) score

The results of the NBTS test scores in groups A and B at the four sample points are shown in Fig 1d. There were no significant differences between groups A and B in the NBTS test scores on day 0 ($P = 0.771$) or day 42 ($P = 0.673$). There were also no significant differences in the NBTS test scores of group A ($P = 0.563$) or group B ($P = 0.933$) dogs between days 0 and 42.

Tests of phagocytic activity

Percentage phagocytic activity

The results of the percentage phagocytic activity scores in groups A and B at the four sample points are shown in Fig 1e. There were no significant differences between groups A and B in the percentage phagocytic activity score on day 0 ($P = 0.122$) or day 42 ($P = 0.999$). There were also no significant differences in the percentage phagocytic activity of group A ($P = 0.999$) or group B ($P = 0.834$) dogs between days 0 and 42.

Ingestion capacity of phagocytic cells

The results of the IP scores in groups A and B at the four sample points are shown in Fig 1f. There were no significant differences between groups A and B in the IP score on day 0 ($P = 0.267$) or day 42 ($P = 0.999$). There were also no significant differences in the IP scores of group A ($P = 0.999$) and group B ($P = 0.800$) dogs between days 0 and 42.

Complete blood counts and biochemical determinations

The values for all standard blood cellular parameters were within the respective reference ranges at days 0 and 42 in both test groups (data not shown).

Similarly, in all dogs in groups A and B, the serum concentrations for creatinine, urea, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and the plasma glucose concentration were within the respective reference ranges on days 0 and 42 (data not

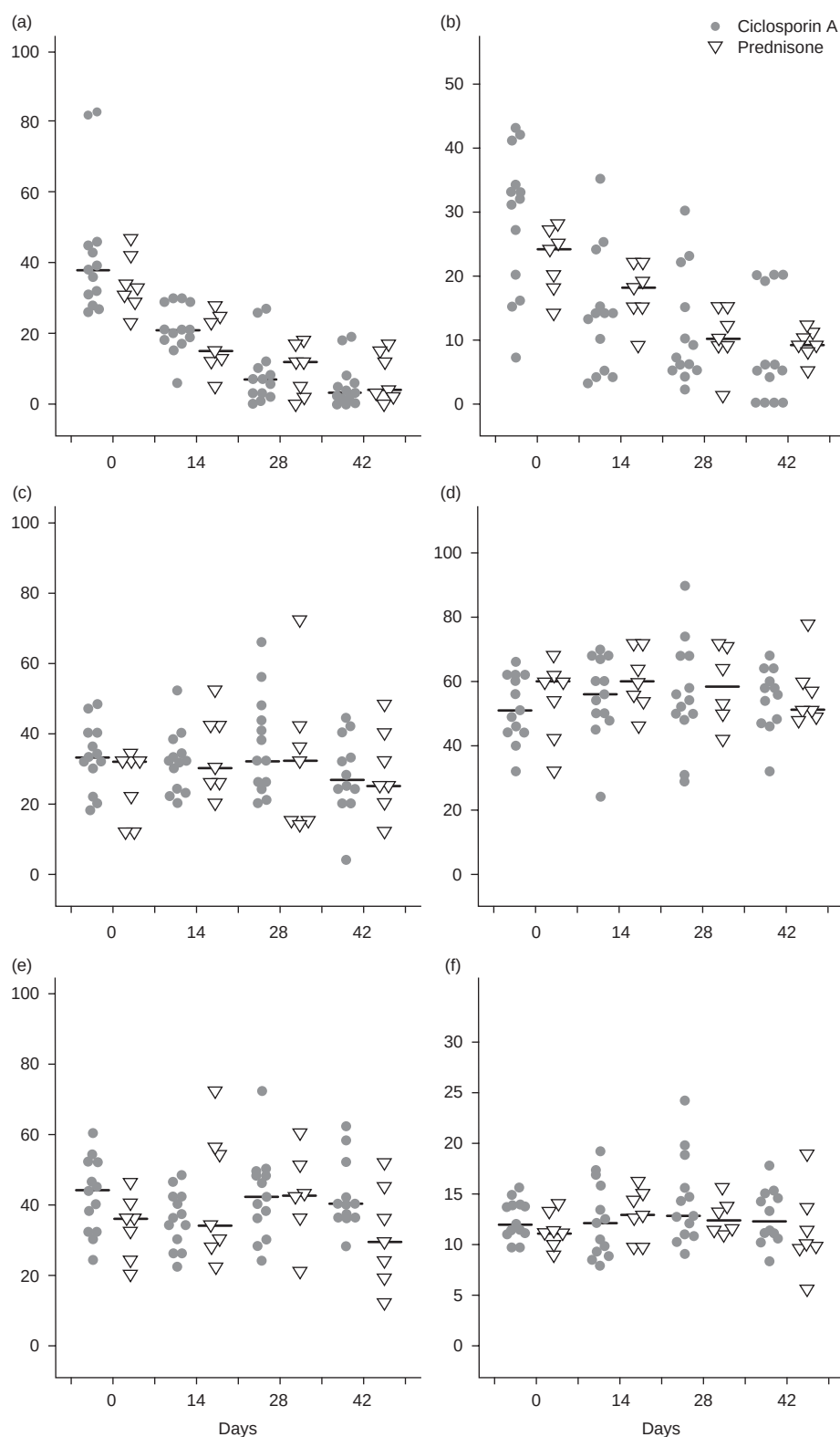


FIG 1: Plots for (a) dynamic changes in the modified canine atopic dermatitis extent and severity index version 1 (mCADESI-01) score, (b) pruritus intensity scale (PIS) score, (c) tetrazolium reductase activity of phagocytes (as measured by the nitroblue tetrazole [NBT] test), (d) zymosan-stimulated tetrazolium reductase activity of phagocytes (as measured by the NBT-stimulated [NBTS] test), (e) phagocytic activity, and (f) ingestion capacity of granulocytes for staphylococci, for 13 dogs treated with ciclosporin A (Equoral oral solution; Teva Pharmaceuticals) and seven dogs treated with prednisone (Encorton; Polfa Pharmaceuticals), measured on days 0, 14, 28 and 42. Horizontal lines indicate the median value

shown). However, a comparison of values obtained on days 0 and 42 revealed that on day 42 there was a statistically significant increase ($P=0.035$) in the concentration of serum urea of prednisone-treated dogs and a significant increase ($P=0.017$) in the concentration of serum aspartate aminotransferase in hgCsA-treated dogs, although these

remained in the reference range. No other significant changes were seen.

Adverse effects

Adverse effects were seen in five (38 per cent) of the 13 dogs in group A. These included intermittent vomiting in three dogs (23 per cent) and diarrhoea or loose stools in two (15 per cent). Adverse effects were seen in all seven dogs in group B, including increased appetite in all seven (100 per cent), polydipsia in all seven (100 per cent) and increased activity in one (14 per cent). In both groups, the signs were mild and resolved at the end of treatment.

Discussion

Canine atopic dermatitis is currently defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens (Halliwell 2006). The treatment of canine atopic dermatitis relies on procedures such as allergen avoidance, which is often difficult or impossible to implement, immunotherapy or pharmacotherapy. A combination approach is usually used (Griffin and Hillier 2001).

Orally administered glucocorticoids are among the drugs most commonly prescribed for the relief of physical signs in dogs with atopic dermatitis. They are standard therapeutic agents as they are highly effective in the majority of cases but, surprisingly, their efficacy has been demonstrated only in a limited number of controlled studies (Olivry and Sousa 2001).

Studies of CsA have demonstrated that it has high efficacy with minimal adverse effects when used in the management of canine atopic dermatitis (Steffan and others 2006). By suppression of cytokine production by helper T cells and by a direct effect on cellular activity, CsA inhibits a number of immunoinflammatory responses that occur following activation of mast cells, Langerhans cells, eosinophils and keratinocytes (Guaguère and others 2004).

Atopica, a microemulsified formulation of CsA licensed for use in dogs, has been available in some European countries since 2002. In others, only human generic versions of ciclosporin are available. These are not licensed for use in dogs and no studies of their efficacy in dogs have been carried out; however, they would potentially be a valuable addition to the veterinary surgeons' armoury.

The present study demonstrates comparable efficacy of hgCsA and prednisone in the treatment of canine atopic dermatitis and indicates that hgCsA is a suitable alternative to prednisone/prednisolone and to the licensed veterinary product in countries where the latter is not available. The observation that there were no significant differences in the reduction of the pruritus and mCADESI-01 scores recorded after treatment with hgCsA or prednisone supports earlier reports comparing prednisolone (Olivry and others 2002) or methylprednisolone (Steffan and others 2003) with

Atopica. In the present study, treatment with hgCsA resulted in a reduction of at least 50 per cent in the mCADESI and pruritus scores of 85 and 77 per cent of dogs, respectively. This is comparable with the results reported for the licensed product, with a reduction of at least 50 per cent in the mCADESI and pruritus scores of 69 to 86.7 per cent and 73.3 to 86 per cent scores, respectively (Fontaine and Olivry 2001, Olivry and others 2002, Thelen and others 2006).

In human beings, the influence of various treatments on the phagocytic activity of neutrophils has been evaluated using various techniques including analysis of the percentage of phagocytosing cells, the phagocytic index and oxygen metabolism (Ahmad and others 2004, Czygier and others 2007). Although a recent study evaluated innate immunity in atopic dogs (Wilkolek and others 2004), to the authors' knowledge, there are no publications investigating the phagocytic function of granulocytes in atopic dogs during ciclosporin or glucocorticoid therapy. The data presented here indicate that over a period of 42 days, neither hgCsA nor prednisone caused a significant reduction in phagocytic activity, as assessed by the NBT and NBTS tests, percentage phagocytic activity and IP.

Clinical reports suggest that the adverse effects of CsA on the natural immunity of canine atopic dermatitis cases are less than those of glucocorticoids, with a significantly lower occurrence of bacterial skin infections, *Malassezia* overgrowth and bacteriuria (Fontaine and Olivry 2001, Olivry and others 2002, Olivry and Mueller 2003, Steffan and others 2003). The failure to detect any significant influence of ciclosporin or prednisone on phagocytic function may be attributable to the small number of atopic dogs in the present study or the relatively short time (42 days) for which the drugs were administered. Studies with a higher number of patients and longer treatment protocol are essential to determine the effects of CsA and prednisone on phagocytic activity when used for the long-term management of canine atopic dermatitis.

There were no significant alterations in the haematological parameters of the dogs in the present study associated with either hgCsA or prednisone treatment. Even short-term treatment with glucocorticoids at the dose used in the present study would have been expected to produce some components of a stress leucogram or disturb the indices of hepatic status – particularly, serum alkaline phosphatase or plasma glucose concentrations. The reasons why this did not occur in the present study are not clear.

The present study failed to detect changes in indices of renal status in dogs treated with hgCsA. By comparison, there was a significant increase in the serum urea concentration in dogs treated with prednisone. The toxicity of CsA in human medicine is well recognised, with nephrotoxicity being the most important and frequently encountered (de Rie and Bos 1997, Faerber and others 2001). It is associated with functional and structural changes in tubules and vessels and may occur even with the administration of low doses (Mason 1990, Young and others 1994). Although a dose-dependent increase in renal arterial resistance and vasoconstriction has been observed in laboratory dogs (Carrier and others 1991), several studies in dogs, including the present one, failed to detect any evidence of CsA-induced nephrotoxicity (Fontaine and Olivry 2001, Olivry and others 2002), even when it was given at a dose of 30 mg/kg/day for 90 days (Novartis 2003).

The use of a generic formulation in clinical practice will increase access to CsA, which plays an important role in the management of canine atopic dermatitis in countries where Atopica, the canine licensed product, is not available. The results of the present study indicate that Equoral oral solution has a similar efficacy to the licensed product and does not appear to be associated with a greater risk of adverse reactions. However, only a small cohort of 13 patients was studied for a relatively short time period. A randomised, double-blinded study comparing the efficacy of Atopica and hgCsA in a greater number of animals and over an extended period of time would be desirable before any final conclusions can be made.

In summary, the frequency of ciclosporin use in the management of canine atopic dermatitis has increased dramatically since the licensing of a product for dogs. However, this product is not easily available or licensed in many countries. Equoral oral solution, the formulation of human generic ciclosporin tested in the present study, is available widely around the world and safety and efficacy comparable to pred-

nison has been demonstrated in the present study. Equoral would, therefore, be an effective alternative to glucocorticoids in the treatment of canine atopic dermatitis in countries where Atopica is not available.

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Evaluation of a human generic formulation of ciclosporin in the treatment of canine atopic dermatitis with in vitro assessment of the functional capacity of phagocytic cells

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