

Comparison of cyclosporine A with methylprednisolone for treatment of canine atopic dermatitis: a parallel, blinded, randomized controlled trial

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Abstract The objective of this multicentre, parallel, blinded, randomized controlled study was to evaluate the efficacy and the safety of cyclosporine (CsA group, 117 dogs) in comparison with methylprednisolone (MP group, 59 dogs) in the treatment of atopic dermatitis for 4 months. Mean induction dose of both drugs (5 mg/kg CsA, 0.75 mg/kg MP) was tapered over time according to the clinical response. At the end of the study, the mean estimated percentage reduction from baseline (confidence interval) of lesion scores was 52% (44–59) and 45% (35–56), and the reduction in pruritus score was 36% (27–43) and 33% (23–43) in dogs in the CsA and MP groups, respectively. These percentages were not significantly different between groups. A significantly better overall assessment of efficacy was obtained in the CsA-treated dogs (76 vs. 63% responses excellent or good in the CsA compared with MP group). CsA-treated dogs presented a higher frequency of gastrointestinal disorders, mainly vomiting, but MP dogs tended to be more susceptible to infections. There was no remarkable change over baseline of the haematological and biochemical parameters in the two groups.

Keywords: allergy, atopic dermatitis, canine, ciclosporin, cyclosporin, cyclosporine, corticosteroids, dog, glucocorticoids, methylprednisolone, randomized controlled trial

INTRODUCTION

The treatment of atopic dermatitis (AD) relies on procedures such as allergen avoidance, prevention of allergen contact, antimicrobial therapy, pharmacotherapy and/or immunotherapy.¹ Pharmacotherapy is frequently needed when a rapid and short-term response is required or when allergen avoidance is difficult or impossible to implement.¹

Orally administered glucocorticoids remain among the most commonly prescribed drugs for the relief of clinical signs in dogs with AD. These drugs are considered as the standard of care as they are highly effective in a majority of cases, despite their proof of efficacy having been tested in only a limited number of controlled studies.² Adverse side effects are seen frequently during long-term glucocorticoid therapy, and such disadvantages have prompted veterinarians to look for alternative treatments. Other anti-inflammatory drugs, such as antihistamines, misoprostol, tacrolimus, phosphodiesterase inhibitors, capsaicin, leukotriene inhibitors and cyclosporine (CsA) have been investigated in clinical trials. The results of the various clinical trials conducted with these substances have been reviewed recently.^{3,4} These evidence-based reviews concluded that there was fair evidence to support the recommendation for using oral

CsA, misoprostol and pentoxifylline in the treatment of canine AD.⁴ More recently, some Chinese herbal preparations were found, in a placebo, randomized controlled trial, to afford moderate relief of clinical signs of canine AD.⁵

CsA was first tested in an uncontrolled experiment of 14 dogs with chronic AD treated with 5 mg/kg once daily for 2 weeks.⁶ At the end of this trial, median pruritus and lesional scores were improved, respectively, by 100 and 60% compared with baseline values. Recently, in a large randomized, blinded, placebo-controlled, multicentre trial, it was established that the daily administration of 5 mg/kg of CsA to dogs with AD significantly improved lesional and pruritus scores compared with placebo, whereas a 2.5 mg/kg dose did not provide significant relief.⁷ Moreover, a randomized blinded trial compared the administration of CsA (5 mg/kg) with that of prednisolone (0.5 mg/kg) in 30 dogs over a 6-week period.⁸ This study confirmed that these drugs were capable of inducing a similar clinical improvement. However, the latter study was of limited scale and duration, and both drugs were administered only for induction, and not maintenance, of remission.⁸

In none of these three trials did CsA administration to dogs cause severe adverse reactions.^{6–8} Reported adverse events were mainly gastrointestinal signs, such as transient emesis or diarrhoea.^{6–8} Specifically, there was no indication of nephrotoxicity, in contrast to what is often reported in human patients. Because of

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this potential effect on renal function in human individuals, it is customary to attempt to taper the inducing dose of CsA during the maintenance phase. Such tapering regimens have proven effective in maintaining the initial remission in human atopic patients.^{9–11}

The two oral glucocorticoids most often used in the treatment of AD are predniso(-ne) (-lone) and methylprednisolone (MP), as these drugs exhibit a short elimination half-life that allows alternate day prescribing modalities. In an open trial, MP was proven highly effective for the treatment of allergic dogs, when administered at 0.4–0.8 mg/kg once daily for 7 days then every other day.¹² Because of the frequent adverse drug reactions seen with glucocorticoid drugs, dose-tapering regimens have been recommended when administered to dogs.¹³ In these treatment protocols, the starting daily dose is first decreased, then given every other day and further tapered whenever possible.¹³ Unfortunately, these dose-tapering schemes have not been investigated in controlled clinical trials enrolling dogs with AD.

The objectives of this trial enrolling dogs with AD were, using a parallel, blinded randomized controlled design:

- 1 To compare CsA with a 'standard of care' oral glucocorticoid (MP).
- 2 To investigate the effect of CsA-tapering regimens in the maintenance phase.
- 3 To evaluate the safety of CsA administration over a 4-month period.

MATERIALS AND METHODS

Study design

This study was designed as a multicentre, parallel, blinded, randomized controlled experiment. Thirty European investigators from Belgium (3 sites), France (12 sites), Italy (4 sites), Spain (4 sites) and the UK (7 sites), most specializing in veterinary dermatology, enrolled subjects into this study. This trial was conducted in compliance with the Procedures and Principles of Good Clinical Practice, as detailed in the European Commission Note for Guidance (III/376792).

Pre-inclusion phase

Study subjects. Client-owned dogs older than 6 months affected with AD were selected for this trial. This disease was diagnosed by fulfilment of published criteria,^{14,15} and elimination of resembling, concurrent or complicating pruritic skin diseases and cutaneous adverse food reactions (allergies or intolerances).

Flea allergy was ruled out by the monthly application of long-lasting adulticides (essentially fipronil or imidacloprid), with concurrent insect growth regulators if deemed necessary by the attending clinician. These treatments were commenced at least 4 weeks before the start of the study. Sarcoptic acariasis (scabies) had been ruled out in all cases using standard

diagnostic and treatment methods, namely, failure to find mites on skin scraping and/or failure to respond to an acaricidal trial using currently accepted products (amitraz/selamectin).

Secondary surface, superficial or deep staphylococcal infections were diagnosed on the basis of clinical signs, with or without cytology. *Malassezia* dermatitis was diagnosed on the basis of clinical signs and cytological evidence of overgrowth using established criteria.¹⁶ In the case of diagnosis of surface, superficial or deep bacterial or *Malassezia* yeast infectious dermatitis, oral antibiotics or ketoconazole were administered for at least 3 weeks until the infection was cleared.

Moreover, an elimination diet was implemented for at least 6 weeks. If the latter had led to a partial reduction of pruritus or skin lesions, dogs were to remain on this diet for the entire duration of this trial. The length of time needed to confirm, by means of an elimination diet, the existence of a cutaneous adverse food reaction remains the subject of debate.¹⁷ Indeed, elimination diets varying in duration from 3 to 13 weeks have been reported.¹⁷ Because of lack of consistent standard for the duration of elimination diets, a period of 6 weeks was deemed consistent with current European practices.

If not performed during the previous 3 months, either intradermal testing or allergen-specific IgE serology was performed to determine the existence of hypersensitivity to environmental allergens.

Finally, a minimum Canine Atopic Dermatitis Extent and Severity Index (CADESI) lesional score (see below for definition) of 25 was required, in order to guarantee sufficient extent and severity of lesions to be able to quantify a clinically relevant therapeutic response.

A wash-out period for drugs known to interfere with the response of the tested therapies was required between their last administration and inclusion in this study. Specific withdrawal times were as follows: oral and topical glucocorticoids or last allergen-specific immunotherapy injection, 2 weeks; injectable long-lasting glucocorticoids or CsA, 8 weeks. Even though the use of antihistamines was prohibited during this trial, withdrawal times before entering the study were not specified because of their minimal efficacy for treatment of canine AD and the short duration of their therapeutic effects.³ When essential fatty acids or vitamin E-supplemented diets had been prescribed to the patients, their administration had to be discontinued 1 week before inclusion into the study, or they had to be continued throughout the entire study. If allergen-specific immunotherapy had been given to the subjects prior to entering this trial, only those dogs whose clinical signs had failed to respond to this treatment regimen were entered in this study. Finally, all drugs known to interfere with the pharmacokinetics of CsA were discontinued, and they had to be replaced with noninterfering medications whenever necessary.

After all preceding inclusion criteria had been satisfied, all owners received detailed information on the study, and they gave written informed consent for their

dog to be entered in this trial. Dogs with seasonal AD could not be included, but there was no exclusion for cases with perennial disease with seasonal exacerbation of clinical signs. Pregnant or lactating bitches, and dogs with a medical condition that could interfere with the evaluation of treatment outcome were excluded from the study.

Sample size estimation. This trial was designed to test the equivalence, i.e. noninferiority, of CsA over one of the most efficient 'standard-of-care' products, MP. Considering that our goal to evaluate the safety of CsA required a sufficient number of subjects, it was decided to treat two-thirds of the population with CsA and one-third with the reference drug MP. Increasing the exposure to the investigation drug was intended to increase the likelihood of observing rare adverse events.

The sample size calculation was established based on the percentage CADESI improvement over baseline, which was considered as the primary end point variable. Previous studies had provided estimates for the standard deviation of this parameter.^{7,8} Based on a lower limit of -12% for difference between test and reference, the power to establish equivalence or superiority was calculated to be at least 90% for group sizes of 60 (MP) and 120 (CsA). In other words, this trial had a 90% confidence that the test substance (i.e. CsA) would be judged to be equivalent or superior if its mean per cent CADESI improvement was at maximum 12 points lower than the mean per cent value of the reference product (i.e. MP).

Study phase

Randomization and blinding. After inclusion, all dogs were allocated to the two treatments according to a randomization list established independently by the statistician and generated by computer software. Randomization was balanced every three cases.

As the tested drugs were presented as differing tablets or capsules, it was not possible to blind the owner. However, the blinding of investigators was maintained by the separation of functions. The investigator was responsible for the clinical evaluation of the subject, while a dispenser delivered independently the drug according to the randomization sequence, adjusted the dose and verified the owner's compliance at each visit. The blinding was to be broken only in case of severe adverse reaction which, in any case, would be followed by withdrawing the case from the study.

Intervention. The test substance (active ingredient) was CsA pro-emulsion concentrate (ATOPICA capsule, Novartis Animal Health, Basel, Switzerland), and it was supplied as soft gelatin capsules of 10, 25, 50 and 100 mg. Methylprednisolone (Oro-Medrol or Medrone V; Pharmacia Upjohn) was available as 2, 4 and 16 mg tablets.

Following randomization, the dogs were assigned to receive one of two treatments: MP (59 dogs), or CsA

(117 dogs) for 4 months. The starting dose of CsA was 5 mg/kg once daily for 4 weeks. The dose of CsA was then tapered over time according to the following scheme: after 4 weeks, a reduction of 51% to 75% of the starting CADESI score resulted in a change to every other day (EOD) dosing. After 8 weeks, a further reduction of > 76% of the score prompted the implementation of a twice a week administration (every third or fourth day). Dose tapering was gradual and reversible (i.e. an increase in the CADESI score could allow the administration frequency to be increased according to the same rules), but it was only possible to halve or double the dose at one time. However, an increase of the CADESI score over baseline led to a withdrawal of the case from this trial. The capsules were administered to fasted animals, at least 2 h before or after feeding.

A similar tapering regimen was used for the administration of MP. The starting dose was 0.5–1 mg/kg once daily for 1 week, then every other day for 3 weeks. The dose was tapered after 4 weeks by reducing the dose to 0.25–0.5 mg/kg EOD if the CADESI score was improved by 51% or more, and it was further decreased after 8 weeks to 0.125–0.25 mg/kg EOD when the improvement was > 76% of the baseline score.

During the course of the study, the oral or topical administration of any anti-inflammatory or antipruritic drug was prohibited. Antibiotics could be used for a maximum of two courses of two weeks each, over the entire study duration. Such short duration of treatment was chosen to reduce the clinical interference of antibiotic administration with the tested drugs. Keratolytic, antiseborrheic and antiseptic shampoos could be applied once a week at most. Finally, any drugs interfering with CsA's metabolism that were required during the course of the study (essentially ketoconazole) were only allowed if given for no longer than two periods of 1 week each.

Assessment of owner's compliance. The verification of the owner's compliance to the established protocol was assessed by looking at the daily record of drug administration, and by counting, at each visit, the number of remaining capsules or tablets. Moreover, a whole blood sample was collected 4 weeks after treatment initiation, to measure the CsA concentration within 24 h of the preceding drug administration. All specimens were sent immediately to Novartis Animal Health Research Center in St Aubin, Switzerland or IDEXX laboratories (Yorkshire, UK). Cyclosporine blood levels were assessed by a fluorescence polarization immunoassay TDx/TDxFLx cyclosporine monoclonal whole blood assay (Abbott Diagnostics, Baar, Switzerland).

Blood count and serum chemistry. To determine whether the administration of the tested drugs modified commonly tested parameters, blood samples were taken for haematology and serum biochemistry at the inclusion and final visits.

Primary and secondary outcome measures

The assessment of efficacy was carried out, primarily, by studying the evolution of skin lesions using a numerical scoring scheme. Owner- and investigator-recorded pruritus and global efficacy assessment scores were used as secondary efficacy variables. All parameters were determined before treatment at inclusion (day 0), and at re-evaluation visits that took place after 4, 8, 12 and 16 weeks.

Lesional score. To estimate the severity of AD in the canine patients, clinicians used a lesion scoring system CADESI as described by Olivry *et al.*⁸ The CADESI consists of an assessment of the severity ('0': none; '1': mild; '2': moderate; and '3': severe) of three different lesions of AD at 40 sites covering the entire body. Clinical signs evaluated included erythema as a marker of acute skin inflammation, lichenification as a sign of chronic cutaneous inflammation and excoriations as an objective lesion for underlying pruritus.

Owner pruritus score. Owners estimated the dog's scratching, during the 3 days preceding the monthly visit, by drawing a mark on a 100-mm visual analogue scale. In this figure, the left-most edge of the line was labelled: 'your dog never scratches or bites himself, or only occasionally as any dog would'. In contrast, 'your dog scratches and bites almost constantly and is in great discomfort' was written on the rightmost end of the line.

Investigator pruritus score. At each re-evaluation visit, investigators estimated the dog's pruritus from 1 ('The dog does not scratch itself, or just scratches from time to time as any dog would') to 5 ('The dog scratches or bites itself constantly').

Global assessment score. At the end of treatment (week 16), or earlier if the dogs were removed from the trial, both investigators and owners rated their perception of treatment efficacy as 'none or poor', 'fair', 'good' or 'excellent'.

Statistical analyses

Intent-to-treat analyses. Because at least one re-evaluation visit was completed by all dogs, data from all study subjects were kept for 'intent-to-treat' analyses. When patients did not complete the trial, the imputation rule for missing data was the 'last value carry forward'. This procedure involves replacing the missing values from the cases not completing the study with the last observed values.

All statistical analyses were performed using SAS Version 6.12 (SAS 1990, 1996). Verification of randomization effectiveness was made by comparing demographic, historical and clinical data using two-sided Fisher's exact test. Assumptions underlying parametric analyses (analyses of variance, ANOVA), i.e. normality of residuals distribution and homogeneity of variance,

also were tested. In cases where they were relevantly violated, transformations were used. The percentage reduction from baseline of CADESI lesion and owner pruritus scores was calculated for each study subject, and the values compared between groups using repeated measures ANOVA. Separate ANOVA with Dunnett's or Cochran-Mantel-Haenszel (CMH) tests were performed for group comparisons, at visits two to four, on both percentage reduction from baseline CADESI and investigator pruritus scores, as well as investigator and owner final global assessments values.

Roles of the authors and conflicts of interest

The leading authors (JS and RF) participated in the design of the trial, interpretation of the data and writing of the manuscript. DA and FB contributed to the study design and follow-up as well as the interpretation of results.

Three authors (JS, DA and FB) are employed by Novartis Animal Health, while the last author (RF) was employed by Novartis Animal Health, Basel Switzerland at the time of the study but performed the statistical analysis as a consultant.

RESULTS

Verification of randomization effectiveness and population characteristics

Thirty investigators enrolled 176 canine patients in this study. No more than 10 dogs (5% of the total number of study subjects) were included by a single investigator. Most of the investigators (27/30) enrolled more than three cases, thus ensuring that treatment groups were adequately distributed between investigators.

Forty-eight breeds of dogs were represented. West Highland White Terriers (19 dogs, 11% of the total population), Labrador Retrievers (17; 10%), Boxers (16; 9%) German Shepherd Dogs (16; 9%), Shar Pei (8; 5%) and Yorkshire Terriers (8; 5%) were the breeds most commonly enrolled. In summary, $\approx 50\%$ of the study subjects came from only six breeds.

Statistical comparisons of the major characteristics of the subject population confirmed that there was no randomization bias in this trial, as sex distribution, weight, housing environment, diet type, historical and baseline clinical parameters were not significantly different between CsA and MP groups (Table 1). Not only were CADESI scores very similar, but so were the lesion characteristics. In both groups, the parameter 'erythema' accounted for $\approx 50\%$ of the total CADESI score, whereas the parameters 'excoriation' and 'lichenification' accounted for $\approx 25\%$ each (data not shown). The mean age at inclusion tended to be slightly lower in the CsA group, but this did not reflect a significantly shorter history of the disease prior to enrolment.

Examination of previous medical records from dogs of both groups revealed a high but comparable prevalence of bacterial skin infections (MP: 40 dogs, 68%; CsA: 87

Table 1. Verification of randomization effectiveness

Parameter	MP	CsA	Test; <i>P</i> -value; significance
Sex distribution; M/F	24/35	55/62	Fisher's; <i>P</i> = 0.52; NS
Age at study onset; years (mean $\pm$ SD)	5.5 $\pm$ 2.8	4.7 $\pm$ 2.4	ANOVA; <i>P</i> = 0.06; NS
Weight at study onset; kg (mean $\pm$ SD)	19.2 $\pm$ 12.4	22.5 $\pm$ 12.9	ANOVA; <i>P</i> = 0.11; NS
Type of housing			
Urban	38	74	Fisher's; <i>P</i> = 0.80; NS
Countryside	19	37	
Other countryside	2	6	
Type of diet fed			
Homemade	12	22	Fisher's; <i>P</i> = 0.39; NS
Commercial	36	80	
Combination countryside	11	15	
CADESI at study onset (mean $\pm$ SD)	69.5 $\pm$ 38	66.8 $\pm$ 30	ANOVA; <i>P</i> = 0.61; NS
Owner's Pruritus Score at study onset (mean $\pm$ SD)	70.3 $\pm$ 22	69.7 $\pm$ 18	ANOVA; <i>P</i> = 0.85; NS
Interval since first diagnosis of AD (months) (mean $\pm$ SD)	38.9 $\pm$ 28.0	34.4 $\pm$ 24.6	ANOVA; <i>P</i> = 0.25; NS

NS, not significant; CADESI, Canine Atopic Dermatitis Extent and Severity Index; ANOVA, analysis of variance.

Table 2. Treatment mean daily dosages and dosing regimen in the CsA group

	Weeks 1–4	5–8	9–12	12–16
Mean daily dose; mg/kg*	4.6	3.53	2.79	2.83
Number (%) of dogs treated				
Daily	117 (100)	54 (52)	28 (28)	30 (32)
EODD	–	48 (50)	58 (58)	39 (42)
TAW	–	–	14 (14)	24 (26)

EOD, every other day; TAW, twice a week.

*Mean dose calculated as the total dose administered between two visits divided by the number of days separating the visits.

dogs, 75%), *Malassezia* yeast infections (MP: 14, 24%; CsA: 29, 25%) or otitis externa (MP: 36, 71%; CsA: 68, 58%). Similarly, the frequency of previous treatments with antibiotics, antifungal drugs, glucocorticoids, allergen-specific immunotherapy as well as antiparasitic medications was also comparable in the two treatment groups (data not shown). In particular, prior treatment with oral glucocorticoids, alone or combined with antihistamines, was reported in 40 (68%) and 72 (62%) subjects of the MP and CsA groups, respectively. Because of the similarity in demographic, environmental, historical and baseline clinical data between the treatment groups, our randomization scheme was considered to be effective.

Verification of owner compliance

Major deviations from the recommended dose ($\pm 20\%$ of the total recommended number of doses over at least 1 month) occurred in 10 subjects in the CsA group and 9 patient dogs in the MP group. Overall, the mean monthly deviation from the prescribed dose fluctuated between -2.8% and $+0.9\%$ in the CsA group and -4.6% and $+6.5\%$ in the MP group.

Using the TDxFlx assay, it was determined that all dogs from the MP groups exhibited blood concentrations of CsA below the analytical limit of quantification of the test (25 ng/mL). Blood concentrations obtained from CsA-treated dogs were all above the detection limit.

In summary, the examination of the owner's log, the assessment of the quantity of drug used and the blood

levels of CsA confirmed that there was an adequate compliance by the owner to the treatment prescribed.

Treatment dose and dosing regimen

Starting treatment dosages were 4.6 and 0.74 mg/kg in the CsA and MP treatment groups, respectively. These dosages were tapered as shown in Tables 2 and 3. In the CsA group, approximately half of the study subjects could be administered the drug on an EOD basis after the fourth week of treatment, and $> 25\%$ could be treated on a twice a week basis at trial's end. A similar pattern was observed in the MP group.

When the clinical signs worsened after a previous dose tapering, a reversion to the previous dosage was required. Such reversion was needed in only a few subjects, and occurred after either 8 weeks (MP: 7 dogs, 14%; CsA: 10 dogs, 10%) or 12 weeks (MP: 7 dogs, 16%; CsA, 20 dogs, 21%).

Drop-out for inefficacy

A drop-out for inefficacy, evidenced by an increase of CADESI scores over baseline value, was observed in 9 subjects (15%) in the MP group, and 10 (9%) in the CsA group. This difference was not significant (Fisher's test; *P* = 0.20). Increased pruritus led to the premature termination of the study in three additional cases (MP: 2 dogs; CsA: 1).

In toto, there were 11 cases in each group (MP: 19%; CsA: 9%) that did not complete this trial because of worsening clinical signs, and the difference between groups neared significance (Fisher's exact test, *P* = 0.094).

Table 3. Treatment mean daily dosages and dosing regimen in the MP group

	Week 1	2–4	4–8	9–12	12–16
Mean daily dose; mg/kg	0.74	0.36	0.29	0.27	0.27
Number (%) of dogs					
SD	57 (100)	–	–	–	–
SD EOD	–	57 (100)	28 (51)	22 (46)	20 (45)
SD/2EOD	–	–	26 (49)	20 (42)	11 (25)
SD/4EOD	–	–	–	5 (10)	10 (23)

SD, starting dose; SD/2, half of starting dose; SD/4, one-quarter of starting dose. EOD, every other day.

Table 4. Percentage improvement over baseline for CADESI lesional scores and owner pruritus scores

	Week 4	8	12	16
CADESI				
CsA	44 (40–49)	53 (47–59)	50 (43–57)	52 (44–59)
MP	44 (38–51)	45 (36–53)	41 (31–51)	45 (35–56)
Pruritus				
CsA	34 (27–41)	39 (32–46)	32 (25–39)	36 (27–43)
MP	46 (36–56)	38 (28–48)	33 (23–43)	33 (23–43)

Data presented as mean estimates (95% confidence intervals).

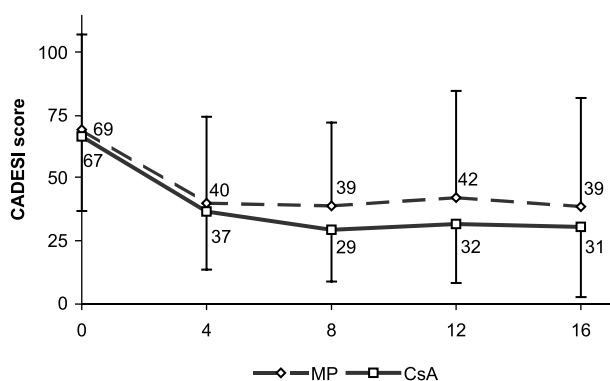


Figure 1. Evolution of mean Canine Atopic Dermatitis Extent and Severity Index (CADESI) lesional scores during the course of the study. The dogs received cyclosporine (CsA, 5 mg/kg daily) or methylprednisolone (MP, 0.5–1 mg/kg daily for 1 week then every other day for 3 weeks) for a month. The dose was then tapered according to the clinical response (see text). Means for all dogs included in the study ($N = 117$ in the CsA group and 59 in the MP group, intent-to-treat analysis).

Nevertheless, data from all dogs, even those that did not finish the trial, remained included for *intent-to-treat* analyses.

Intent-to-treat analyses (ITT)

Treatment effect on lesional scores. In both groups of subjects, CADESI lesional scores improved markedly during the first 4 weeks of this trial. In MP-receiving dogs, scores remained stable for the following 12 weeks, whereas they continued to decrease slightly in the CsA group for another 4 weeks before reaching a plateau (Fig. 1).

The mean percentage reduction from baseline of CADESI scores neared 45% in the MP group, whereas it varied from 45 to 52% after four weeks in the CsA group.

At the end of the study, an improvement of CADESI scores $\geq 50\%$ was seen in 34/59 (58%) and 77/117 (66%) dogs of the MP and CsA groups, respectively. In contrast, a worsening of this score (i.e. negative percentage change from baseline) was found in 10/59 (17%) and 17/117 (15%) in the MP and CsA groups. These responses were not significantly different between groups ($P = 0.47$; CMH trend test).

All the components of the CADESI score improved by $> 50\%$ in the two groups at trial's end. The median rates of improvement were 56 and 56% for the parameter 'erythema', 67 and 72% for 'lichenification', and 69 and 79% for 'excoriation' in the MP and CsA groups, respectively. Medians reflected the overall response better than the means, as there were outliers in the MP group with a very marked deterioration of the excoriation score. The corresponding mean values for erythema, lichenification and excoriation were 45, 22 and 49% in the MP group, and 47, 55 and 62% in the CsA group, reflecting a more consistent response in the CsA group.

The 95% confidence intervals for the CADESI improvement over baseline are given in Table 4. Non-inferiority at the 5% level was proven at all time points. Repeated measures ANOVA on percentage CADESI improvement did not show any significant differences between the treatment groups ($P = 0.18$ for the group effect and 0.22 for time–group interactions).

Treatment effect on investigator and owner pruritus scores

During this study, investigator pruritus scores decreased markedly in both groups during the first 4 weeks of treatment, and they remained stable thereafter. The frequency of severe pruritus (score 4 or 5) decreased from $\approx 65\%$ to $< 25\%$ in both groups after 4 weeks and did not change further until the end of the study (Table 5). An increase of pruritus severity was

Table 5. Investigator pruritus scores: evolution of percentage of subjects with differing pruritus severity over time

Weeks	CsA mild	severe	MP mild	severe	P-value
0 (initial)	6.0	65	2	64	0.82
4	47	20	64	19	0.18
8	52	22	56	20	0.82
12	47	24	56	22	0.74
16 (end)	51	25	58	17	0.34

Mild is defined as total frequency of scores 1 and 2, severe as total frequency of scores 4 and 5.

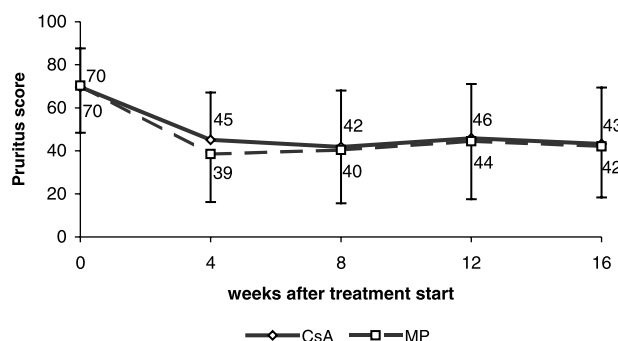


Figure 2. Evolution of the mean owner pruritus scores (visual analogue scale) during the course of the study. The dogs received cyclosporine (CsA, 5 mg/kg daily) or methylprednisolone (MP, 0.5–1 mg/kg daily for 1 week then every other day for 3 weeks) for a month. The dose was then tapered according to the clinical response (see text). Means for all dogs included in the study ($N = 117$ in the CsA group and 59 in the MP group, intent-to-treat analysis).

noted in only 7 (12%) and 8 (7%) dogs in the MP and CsA groups, respectively. There was no significant difference between groups in terms of pruritus severity at any time point (CMH trend test).

Analyses of owner pruritus scores, established with a visual analogue scale, yielded similar results (Fig. 2). A slightly faster improvement in scores was observed in the MP group initially, but there were similar improvements in both groups thereafter. There were no significant differences between groups ($P = 0.60$; ANOVA) or any time–treatment interaction (ANOVA; $P = 0.11$) effects.

At the end of the study, an improvement of owner pruritus scores $\geq 50\%$ was seen in 25/59 (42%) and 47/117 (40%) dogs of the MP and CsA groups, respectively. In contrast, a worsening of this score (i.e. negative percentage change from baseline) was found in 12/59 (20%) and 25/117 (21%) in the MP and CsA groups, respectively. These responses were not significantly different between groups ($P = 0.69$; CMH trend test).

The estimates as well as the lower and upper limits of the confidence intervals of the percentage reduction of owner pruritus scores are presented in Table 4. Reported values were not significantly different between groups.

Overall and at the final visit, owner and investigator pruritus scores change from baseline were correlated significantly ($r = 0.72$; $P < 0.0001$; Pearson's correlation test). There was also a strong correlation in the changes over baseline of CADESI and both pruritus scores ($r = 0.48$ and 0.50 for the owner and investigator scores, respectively, $P < 0.0001$; Pearson's correlation test).

Investigators' global assessment of efficacy

At study end (week 16), the global efficacy of treatment was evaluated by the clinicians as good-to-excellent in 36/57 (63%) and 85/112 (76%) subjects of the MP and CsA groups, respectively (two and five cases with premature termination were not assessed in the MP and CsA groups, respectively). The rate of 'treatment failure' (as rated by no response or deterioration of clinical signs) was higher in the MP group (12% of dogs) than in the CsA group (8%). Overall, the response to CsA was significantly better than that to MP ($P = 0.03$; CMH trend test).

A significant correlation was found between the investigators' global assessment of efficacy and the final percentage improvement over baseline of CADESI scores ($r = 0.62$, $P < 0.0001$; Pearson's correlation test). Similar correlations were observed, at the final visit, between the investigators' global assessment of efficacy and per cent improvement over baseline of both investigators' and owners' pruritus scores ($r = 0.57$ and 0.53 , respectively; $P < 0.0001$; Pearson's correlation test).

Owners' global assessment of efficacy

Owner assessment of efficacy was very similar to the investigator with a good-to-excellent response in 34/57 (60%) and 83/112 (75%) subjects of the MP and CsA groups, respectively. The rate of treatment failure as defined above was also higher in the MP group (17% of dogs) than in the CsA group (9%). The distribution between groups was significantly different ($P = 0.02$, CMH trend test).

Assessment of treatment safety

Adverse events. All adverse events, whatever severity or duration, suspected to be, or not to be related to drug administration, were recorded during the study. There was a similar frequency of adverse events in the two groups (80 and 81% in MP and CsA groups, respectively). Most events were rated as mild or moderate (75 and 85% in MP and CsA groups, respectively). The frequency of the various adverse events is given in Table 6.

Gastrointestinal disorders (e.g. emesis, diarrhoea, soft stools) were the adverse events most commonly noticed in CsA-treated dogs, and their frequency was higher in the CsA than in the MP group. Emesis was recorded at least once in 43 dogs (37%) of the CsA group, but it was seen sporadically in most patients and

Table 6. Frequency of adverse events

Type of adverse event	CsA group (117 dogs)	MP group (59 dogs)	P-value*
Gastrointestinal disorders including:	55 (47%)	15 (25%)	0.006
Emesis	43 (37%)	5 (9%)	0.0001
Diarrhoea	21 (18%)	9 (15%)	0.83
Others	10 (8%)	2 (3%)	0.34
Skin infections including:	34 (29%)	20 (34%)	0.60
Uncharacterized skin infection (pyoderma)	16 (14%)	15 (25%)	0.045
Folliculitis	11 (9%)	3 (5%)	0.39
Pyotraumatic dermatitis	2 (2%)	0 (0%)	0.55
Malassezia infections	13 (11%)	4 (7%)	0.42
Others	1 (1%)	1 (2%)	1.0
Other non infectious dermatological diseases	7 (6%)	2 (3%)	0.72
Otitis	9 (8%)	5 (8.5%)	1.0
Conjunctivitis	1 (0.9%)	1 (1.7%)	1.0
Other infectious diseases	4 (3.4%)	1 (1.7%)	0.66
Polyuria-Polydypsia	5 (4.3%)	15 (25%)	< 0.001
Increased appetite and body weight	4 (3%)	7 (12%)	
Others			
Decreased appetite	5 (4%)	0 (0%)	0.17
Gingival hyperplasia	3 (3%)	0 (0%)	0.55
Events related to the reproductive behaviour	7 (6%)	3 (5%)	1.0
Miscellaneous	25 (21%)	9 (15%)	0.42

*Two-tailed Fisher's exact test.

†Several adverse events may be reported for one dog; data reported as number (percentage of cases).

for a total number of days of fewer than 3 in 26/43 of the dogs over the study duration. Diarrhoea was seen with a similar frequency in the two groups. Following repeated vomiting and/or diarrhoea, CsA treatment had to be interrupted in 7/117 cases (6%). Another subject with persistent abdominal pain of unknown origin was also removed from the study. All cases recovered spontaneously shortly after treatment discontinuation.

Bacterial or fungal dermatitis, otitis or conjunctivitis were diagnosed with a similar frequency in the two groups. Infections were considered severe or very severe in 7/20 (35%) in MP-receiving dogs vs. 5/34 subjects (15%) of the CsA group. Drop-out from the study because of uncontrolled bacterial infections was needed twice more frequently in the MP than in the CsA group (eight subjects in each group, e.g. 14 vs. 7%).

MP-receiving dogs presented more frequently with polyuria, polydypsia (15 dogs, 25%) and increased appetite or weight gain (7 dogs; 12%). In contrast, such signs developed in five (4%) and four dogs (3%) in the CsA group. The differences in these percentages was significant ($P = 0.001$; Fisher's exact test). Gingivitis and decreased appetite were recorded in the CsA group in five (4%) and three (3%) subjects, respectively.

Effect on haematology and serum chemistry

A significant change from mean baseline values of creatinine and urea serum levels was not seen in either group. In only one dog of the CsA group was post-treatment serum glucose was higher than the pretreatment value. After treatment, serum potassium concentrations were significantly and consistently higher in CsA-receiving dogs (+0.60 mg/dL), but lower in the MP

group (−0.65 mg/dL). However, post-treatment mean potassium concentrations remained within normal values (median baseline concentration were 17 mg/dL and 18 mg/dL, range 14–27 and 12–24 mg/dL in the MP and CsA groups, respectively). Also, a small increase of cholesterol over baseline concentrations was found in both groups (+0.37 and 0.19 g/L in MP and CsA groups, respectively), but this change was perceived to be of no clinical relevance (median baseline concentration: 2.1 and 1.8 g/L; range 0.9–7 and 0.7–5 in the MP and CsA groups, respectively).

There was no marked change in haematological parameters over baseline in the two groups.

Concurrent treatments

Glucocorticoids were used only in a few dogs (Table 7), in case of intense pruritus or in emergency situations (e.g., a herniated disc in one dog of the MP group). Glucocorticoid administration was followed by withdrawal from the study.

Approximately one third of subjects from both groups received systemic antibiotics (usually cephalexin or fluoroquinolones), and in one-tenth of cases, they were given topical antibiotics. Systemic antibiotics were almost always prescribed for skin infections except in rare cases in which they were given for otitis or infections of other organs. In all but a few of these subjects (six in the CsA and four in the MP group), treatment duration did not exceed two consecutive weeks.

Oral or topical antifungal drugs, which included ketoconazole, were administered for < 7 days in 11 dogs and for > 7 days in only 3 cases. Shampoos, which usually consisted of antiseborrheic or cleansing formulations, were used in dogs from both groups, for a single occasion or every 2 weeks.

Table 7. Concurrent treatments used during the trial

Treatments	CsA Group	MP Group	P-value*
Glucocorticoids (any formulation)	3 (3%)	2 (7%)	1.00
Antibiotics (systemic)	33 (28%)	19 (32%)	0.60
Antibiotics (topical)	9 (8%)	7 (12%)	0.41
Antifungals (systemic, topical)	10 (9%)	4 (7%)	0.78
Ear and eye drops (antibiotics $\pm$ glucocorticoids)	8 (7%)	2 (3%)	0.50
Ear cleansers	10 (9%)	7 (12%)	0.59
Shampoos or antiseptic lotions	32 (27%)	21 (36%)	0.30
Gastrointestinal treatments	14 (12%)	3 (5%)	0.18
All others†	37 (32%)	12 (20%)	0.15

*Two-tailed Fisher's exact test.

†Vaccines, internal antiparasitics, nutritional, vitamin and mineral supplements, nonsteroidal anti-inflammatory agents, topical anaesthetic drugs.

DISCUSSION

In this study enrolling dogs with AD, the efficacy of CsA was found to be equal to that of MP based on the objective clinical parameters, but it was perceived to be better than MP by the investigators and the owners on their global assessment of efficacy. This trial was designed to test for equivalence and not superiority of the tested drug over the 'standard of care' medication. Thus, the power of the statistical tests employed was insufficient to prove a significantly higher improvement of CsA over MP although there was a greater reduction in CADESI lesional scores in CsA-receiving dogs. Despite this caveat, a significantly better global assessment was given to CsA than to MP. Such evaluation could reflect a lower rate of 'nonresponding' dogs in the CsA group and/or an improvement in quality-of-life issues, an assessment that is difficult to quantify in dogs, but that has often been reported in human patients with AD prescribed CsA.^{18,19}

This large-scale study, conducted on a representative population of dogs with AD, provides evidence that, at this time, CsA is one of the most powerful drugs in the treatment of AD. Indeed, none of the previously tested antihistamines,³ anti-inflammatory drugs⁴ or Chinese herbal preparations⁵ have, to date, demonstrated a similar antiallergic potency.

The results of this trial are consistent with those of earlier studies in which the same parameters were used for the clinical evaluation. In these reports, the percentage reduction from baseline of CADESI values was 58 and 68%.^{7,8} In comparison, our intent to treat analysis yielded a slightly lower improvement in the this trial (44–53% depending on time points). Nevertheless, the investigators' global evaluation were similar between trials: 76% of the responses were judged excellent or good in this study compared with 74% in nonseasonal subjects of the placebo-controlled experiment.⁷

In this study, the response of clinical signs of AD to oral glucocorticoids (45% reduction in lesional scores) was lower than reported previously. In an open trial, Guaguère *et al.* obtained > 75% improvement in three-quarters of the dogs treated with MP at 0.4–0.8 mg/kg for 2 weeks.¹² Later, Ferrer *et al.* observed a reduction of lesional scores of $\approx$ 60% in prednisolone-treated

dogs,²⁰ and similar results were reported by Olivry *et al.* with 0.5 mg/kg of prednisolone administered for 6 weeks.⁸ In this study, there was a 50% improvement over baseline of the lesion score.

Intent-to-treat analyses, which include all cases evaluated at least once, are more likely to mirror treatment effects observed in clinical practice. In such schemes, noncompliant and nonresponding subjects remain available for analysis and missing values are replaced with the last observation given before withdrawal. In contrast, *per protocol analyses* exclude patients which do not meet entry criteria, those that deviate severely from the study protocol, or those that are excluded because of adverse events. Such schemes closely reflect the protocol under evaluation, but they usually provide an overoptimistic evaluation of the treatment's efficacy. In support of this concept, a recent meta-analysis of clinical trials enrolling human patients with psoriasis or AD yielded a 11–16% higher treatment efficacy when evaluating *per protocol* compared to *intent to treat* analyses.²¹

Dose-tapering regimens are a common practice in human medicine as creatinine serum levels, as well as blood pressure measurements, are often increased following CsA administration. In patients with AD, the dose of CsA is often tapered by reducing the daily dose,¹⁰ but every-other-day administration is probably more effective in controlling clinical signs.⁹ Considering the relatively long half-life of CsA in the canine species^{22,23} and the convenience of such mode of administration, an alternate-day regimen was selected for this trial. Improving owner's compliance by the reducing the frequency of administration was the principal objective of the dose tapering, as renal function impairment is an uncommon adverse reaction of CsA in dogs.^{7,8,24}

In this trial, CsA could be administered every other day in approximately half of treated dogs after an induction of 4 weeks, and one-quarter of subjects completed the trial with an administration of CsA twice a week. Consequently, the starting daily dosage decreased from 4.6 mg/kg in the induction phase to 2.8 mg/kg during the last month of the study. Therefore, the daily dose, as well as response rate, during maintenance CsA therapy appear to be very similar in both dogs and humans with AD.^{9,10,25}

A standardization of the evaluation of clinical response to tested therapies is essential for a valid evaluation and comparison of drug efficacy. The lack of a consistent evaluation scheme can complicate the interpretation of treatment response, as noted in a recent double-blind study in which differing and independent evaluation of clinical parameters by both owner and clinician investigators led to inconclusive results.⁵ Our study further established that the CADESI scoring system provides a reliable and objective measurement. Indeed, the CADESI composite score takes into account not only erythema, but also excoriation and lichenification that each accounted for 25% of the total initial lesion score in this study. Moreover, not only erythema but also excoriation and lichenification have to be considered for a full evaluation of the clinical response. In this study, the overall assessment of efficacy given by the investigators correlated equally with the improvement over baseline of both CADESI and owner's pruritus scores. Such analysis demonstrates that these two parameters play an almost identical role in the evaluation of efficacy. We propose that both parameters should be considered as primary end-point variables in future clinical trials evaluating the efficacy of antiallergic drugs in dogs.

Vomiting is the most frequent adverse reaction that occurs after CsA administration to dogs.^{6–8,24} In our study, emesis appeared often in the first few days of treatment, and it was usually transient. The reasons for the cause(s) of CsA-induced vomiting and the observed individual susceptibility remain unknown.

Herein, we confirmed in a large dog population that the administration of CsA does not lead to an increase in renal function parameters, as seen commonly in human individuals.²⁶ Moreover, creatinine and blood urea nitrogen parameters were also stable in previous studies of short-term CsA administration at the same dosage^{6–8} or at a higher dosage of 14 mg/kg daily for up to 24 weeks.²⁷

Gingival hyperplasia, probably recorded as gingivitis by the investigators, has been reported in dogs treated with high-dose CsA.²⁸ It is suspected to have been induced by the drug in the three dogs in this study.

Glucose levels increased markedly in one dog treated with CsA, $\approx$ 3 months after inclusion in this study. A reversible dose-dependent inhibition of insulin secretion has been reported after CsA administration to dogs,^{29,30} but increased glucose levels remarkably have never been observed in a long-term toxicological study,²⁴ in previous clinical trials, or in all other dogs given CsA in this study. The diabetic dog of this trial presented with vomiting, weight loss and polydipsia soon after inclusion, this early appearance suggesting that the disease could have existed before the trial's onset.

The high frequency of bacterial and *Malassezia* skin infections observed in this trial is not surprising, as dogs with AD are known to be susceptible to such infections.³¹ Similarly, skin infections were reported recently in 57% of dogs with AD given placebo for 6 weeks, although the rate of infection was reduced to 25% in dogs receiving a moderately active substance.⁵

In this study, the prevalence of skin infections decreased from 50 and 46% (during the 4 months before inclusion) to 29 and 33% (during the trial) in dogs given CsA or MP, respectively. These observations suggest that an effective control of the clinical signs of canine AD could lead to a reduction of the frequency of skin infections.

It is not surprising that the only noticeable adverse events observed during MP administration were polyuria, polydipsia, polyphagia and an increase in body weight, as these signs are the most common adverse reactions seen after glucocorticoid administration.² With high doses of glucocorticoids used over long periods, more severe adverse effects can appear such as urinary tract infections,³² pancreatitis, gastrointestinal ulceration, muscle and skin atrophy, inhibition of hypothalamic–pituitary adrenal axis function and finally iatrogenic Cushing's syndrome.² Such severe adverse reactions of glucocorticoids were not seen in our trial, because of the short treatment duration and the rapid dose reduction scheme. Nevertheless, MP-treated dogs seemed more susceptible to infections than those receiving CsA, as the frequency and severity of infections, frequency of antibiotic treatment and drop-out because of infections were higher than in the other group. However, these frequencies were not significantly different between groups.

In conclusion, this large-scale study provided randomized controlled trial-grade evidence that CsA monotherapy is equivalent to MP administration for treatment of AD in dogs. Moreover, our results suggest that the inducing dosage of 5 mg/kg can be tapered over time, while treatment efficacy is maintained, with a dose at least twice lower than that needed during the induction phase. The most frequent adverse reactions seen during CsA therapy were gastrointestinal disorders, chiefly intermittent vomiting, but otherwise this treatment was well-tolerated.

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Résumé Le but de cette étude contrôlée, multicentrique, parallèle, en aveugle et randomisée, était d'évaluer l'efficacité et l'inocuité de la cyclosporine (groupe CsA, 117 chiens) en comparaison de la méthylprednisolone (groupe MP, 59 chiens) pour le traitement de la dermatite atopique pendant 4 mois. La dose moyenne d'induction pour les deux molécules (5 mg kg^{-1} CsA, 0.75 mg kg^{-1} MP) était progressivement diminuée en fonction de la réponse clinique observée. A la fin de l'étude, le pourcentage moyen de réduction des scores lésionnels et les intervalles de confiance étaient de 52% (44–59) pour le groupe CsA et de 45% (35–56) pour le groupe MP, alors que le pourcentage moyen de réduction du prurit était de 36 % (27–43) pour la CsA et de 33% (23–43) pour la MP. Ces pourcentages ne sont pas significativement différents entre les groupes. L'amélioration a été jugée significativement meilleure dans le groupe CsA (76% vs 63% des réponses étaient cotées excellentes ou bonnes dans le groupe CsA comparé au groupe MP). Les chiens traités par la CsA ont présenté significativement plus de troubles gastro-intestinaux (notamment des vomissements) mais les chiens du groupe MP se sont avérés plus sensibles aux infections. Aucune modification remarquable des paramètres hématologiques ou biochimiques n'a été remarquée dans les deux groupes de chiens.

Resumen El objetivo de este estudio multicéntrico, en paralelo, ciego y al azar controlado fue evaluar la eficacia y seguridad de la ciclosporina (grupo CsA, 117 perros) en comparación con la metilprednisolona (grupo MP, 59 perros) en el tratamiento de dermatitis atópica durante 4 meses. La dosis media de inducción para ambas drogas (5 mg kg^{-1} CsA, 0.75 mg kg^{-1} MP) fue disminuida con el tiempo de acuerdo con la respuesta clínica. Al final del estudio, el porcentaje de reducción medio estimado desde la línea basal (intervalo de confianza) de la puntuación de las lesiones fue del 52% (44–59) y 45% (35–56), y la reducción de la puntuación del prurito fue del 36% (27–43) y 33% (23–43) en los perros de los grupos de CsA y MP, respectivamente. La diferencia entre los porcentajes de ambos grupos no fue significativa. En la estimación global, la eficacia fue mejor en el grupo de perros tratados con CsA (76% de respuestas excelentes o buenas en el grupo CsA comparado con el 63% en el grupo MP). Los perros tratados con CsA mostraron una mayor frecuencia de alteraciones gastro-intestinales, principalmente vómitos, mientras que los perros tratados con MP presentaron mayor susceptibilidad a infecciones. No se observaron diferencias remarcables en los niveles basales de los parámetros hematológicos y bioquímicos en ambos grupos.

Zusammenfassung Das Ziel dieser parallelen, randomisierten und kontrollierten Multicenterblindstudie war die Bewertung der Wirksamkeit und Sicherheit von Zyklosporin (ZsA Gruppe, 117 Hunde) im Vergleich mit Methylprednisolon (MP Gruppe, 59 Hunde) in der Behandlung der atopischen Dermatitis für 4 Monate. Die mittleren Induktionsdosen beider Medikamente (5 mg kg^{-1} ZsA, 0.75 mg kg^{-1} MP) wurden mit der Zeit abhängig von der klinischen Wirksamkeit verringert. Am Ende der Studie betrug bei Hunden in der ZsA und der MP Gruppe die mittlere geschätzte prozentuale Reduktion von den Basiswerten (und das Konfidenzintervall) der Läsionswerte 52% (44–59) und 45% (35–56) und die Reduktion des Juckreizwertes 36 % (27–43) und 33% (23–43). Diese Prozentzahlen unterschieden sich nicht signifikant zwischen den beiden Gruppen. Eine signifikant bessere Gesamtbewertung wurde bei mit ZsA behandelten Hunden gesehen (76% gegenüber 63% exzellenten oder guten Ergebnissen in der ZsA verglichen mit der MP Gruppe). Mit Zyklosporin behandelte Hunde hatten häufiger Gastrointestinalbeschwerden (hauptsächlich Erbrechen), aber die mit MP behandelten Hunde tendierten zu höherer Infektionsempfänglichkeit. Es gab keine bemerkenswerte Abweichungen von den Basiswerten in hämatologischen und biochemischen Parametern in den beiden Gruppen.