

Randomized controlled trial of the efficacy of cyclosporine in the treatment of atopic dermatitis in dogs

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Objective—To evaluate efficacy of cyclosporine A, administered at either of 2 dosages, in dogs with atopic dermatitis (AD).

Design—Multicenter randomized controlled trial.

Animals—91 dogs with AD.

Procedure—Dogs were assigned to receive placebo (30 dogs), cyclosporine at a low dosage (2.5 mg/kg [1.1 mg/lb], PO, q 24 h for 6 weeks; 30 dogs), or cyclosporine at a high dosage (5.0 mg/kg [2.3 mg/lb], PO, q 24 h for 6 weeks; 31 dogs).

Results—After 6 weeks, mean percentage reductions, compared with baseline scores, in scores of lesion severity were 34, 41, and 67% for dogs treated with the placebo, cyclosporine at the low dosage, and cyclosporine at the high dosage, respectively. Similarly, mean percentage reductions in pruritus scores were 15, 31, and 45%, respectively. Percentage reductions in skin lesion and pruritus scores were significantly higher for dogs given cyclosporine at the high dosage than for dogs given the placebo. Treatment efficacy was significantly associated with whether dogs had a history of seasonal AD. Percentage reductions in skin lesion and pruritus scores were high for dogs treated with cyclosporine at the highest dosage that had a history of nonseasonal AD. Dogs in all groups with seasonal AD improved during the study period.

Conclusions and Clinical Relevance—Results suggest that oral administration of cyclosporine at a dosage of 5.0 mg/kg once daily is effective in reducing severity of pruritus and skin lesions in dogs with AD, especially those with nonseasonal disease. (*J Am Vet Med Assoc* 2002;221:370–377)

In humans and dogs, atopic dermatitis (AD) is a common, chronic, relapsing allergic skin disease. Affected individuals typically have pruritic erythema-

tous lesions, as well as secondary skin lesions at flexure and friction areas.¹⁻³ Albeit not fully elucidated, the pathogenesis of AD in humans and dogs appears to be multifactorial. Lesions are thought to result from flare factors (eg, allergens and microbes) triggering a complex interplay of IgE reagenic antibodies, antigen-presenting cells, T lymphocytes, eosinophils, and mast cells.⁴⁻⁷

Successful management of AD in human patients requires a multifaceted approach that includes increasing skin hydration and identifying and avoiding flare factors such as irritants, allergens, microbes, and stress.^{8,9} When skin lesions interfere with quality of life, treatment with anti-inflammatory pharmacologic agents is instituted.^{8,9} A recent meta-analysis evaluated randomized controlled trials studying efficacy of various treatments in humans with AD.¹⁰ The only treatments for which there was reasonable evidence of efficacy were topical administration of glucocorticoids, oral administration of cyclosporine, and ultraviolet light therapy.¹⁰ Remarkably, glucocorticoids, cyclosporine, and ultraviolet light share the capability to repress activation of various immune cell types known to be involved in the pathogenesis of AD.

The dosage of cyclosporine proven to be effective for treatment of AD in humans is variable. Whereas early clinical trials established that cyclosporine administered at a dosage of 5.0 mg/kg (2.3 mg/lb, PO, q 24 h) satisfactorily controlled signs of AD,^{11,12} other authors reported that administration at a lower daily dosage (2.5 mg/kg [1.1 mg/lb]) was sufficient to induce remission.¹³ A similar dosage range also has been proposed to treat human patients with psoriasis, another immune-mediated skin disease.¹⁴

Treatment of AD in dogs also requires a systematic multifaceted approach, which can involve 1 or more of the following steps: allergen avoidance and prevention of allergen contact, administration of anti-inflammatory agents, allergen-specific immunotherapy, and treatment with antibacterial and antifungal drugs.¹⁵ Veterinary clinicians can elect to combine these therapeutic steps in various orders, depending on their perception of the relative importance of triggering factors to development of lesions in individual patients.

Because oral administration of cyclosporine has been shown to be efficacious in decreasing pruritus and severity of skin lesions in human patients with AD,¹⁶ its efficacy in dogs has also been examined. A 2-week study¹⁷ of 14 dogs with AD provided preliminary evidence of the efficacy of cyclosporine treatment (5.0

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The authors thank Drs. Fabienne Brovedani, Didier Leffay, and Beatrice Besche for monitoring the clinical trial; Didier Sevestre for managing the data; and Margrit Kunz for performing cyclosporine assays.

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mg/kg, PO, q 24 h). A 6-week randomized controlled trial¹⁸ further established the efficacy of cyclosporine at this dosage for treatment of dogs with AD. In these 2 studies, however, the dosage of cyclosporine was extrapolated empirically from clinical trials of human patients with AD,^{11,12,16} with the knowledge that the pharmacokinetics of cyclosporine in humans and dogs are similar.^{19,20}

The purposes of the study reported here were to compare the efficacy of cyclosporine, administered at either of 2 dosages, with the efficacy of a placebo in dogs with AD and to determine which of these 2 dosages of cyclosporine would be more effective.

Material and Methods

Study design—The study was designed as a multicenter, multi-investigator, parallel, double-blind, randomized controlled trial. It was conducted in compliance with the Procedures and Principles of Good Clinical Practice, as detailed in the European Commission Note for Guidance (III/376792). Sixteen European investigators, most of them specialized in dermatology, enrolled patients in the study.

Inclusion criteria—Client-owned dogs with AD were eligible for inclusion in the study. In these dogs, the diagnosis of AD was made on the basis of a compatible history and fulfillment of standard clinical criteria.²¹ In addition, all similar-appearing pruritic skin diseases, such as flea allergy dermatitis, sarcoptic acariasis (scabies), cutaneous adverse food reactions (allergy or intolerance), and superficial or deep bacterial or *Malassezia* yeast dermatitis, were carefully ruled out, according to standard diagnostic and treatment methods.

In all dogs, a topical flea adulticide with a minimum 1-month duration of activity was applied for at least 1 month before and monthly throughout the study. Insect growth regulators and development inhibitors were used as desired. All dogs were fed an elimination diet; if this resulted in a partial reduction in severity of pruritus or skin lesions, dogs remained on this diet for the duration of the study. If not done during the previous 3 months, either intradermal testing or allergen-specific IgE serologic testing was performed to confirm hypersensitivity to environmental allergens.

Oral and parenteral administration of long-lasting corticosteroids was discontinued at least 1 and 3 weeks, respectively, prior to the beginning of the study. In dogs receiving essential fatty acids, administration was discontinued 4 weeks prior to the beginning of the study or was continued throughout the entire study period. Finally, administration of all drugs known to interfere with the pharmacokinetics of cyclosporine (eg, ketoconazole, erythromycin)²² was discontinued; medications that did not interfere with cyclosporine pharmacokinetics were substituted when necessary.

Owners of dogs considered for inclusion in the study received detailed information on the study and provided written informed consent.

Exclusion criteria—Pregnant or lactating dogs, dogs with a medical condition that could interfere with the evaluation of treatment outcome, dogs with an uncontrolled bacterial or fungal infection of any organ, and dogs with concurrent uncontrolled adverse food reactions or flea allergy dermatitis were excluded from the study. Moreover, so that meaningful improvement in clinical signs could be detected during the study, dogs in which the baseline skin lesion score was < 25 were also excluded.

Sample size estimation—Interindividual variability of clinical parameters of AD was estimated from a previous study¹⁸ in which similar skin lesion and pruritus scoring

schemes had been used. For the present study, it was calculated that at least 14 dogs were needed in each group to have a 90% chance of detecting significant ($P < 0.05$) differences of 50% or greater between dogs treated with cyclosporine and dogs treated with a placebo.

Randomization—Ninety-one dogs with AD were included in the study. All dogs were assigned to 1 of 3 groups by an independent data manager by use of randomization computer software.

Experimental protocol—The test substance was cyclosporine A proemulsion concentrate supplied as a solution (100 mg of cyclosporine/ml) for oral administration.^a The placebo consisted of the same solution without the active ingredient.

Dogs were randomly assigned to receive 1 of 3 treatments: placebo (0.025 ml/kg [0.011 ml/lb], PO, q 24 h; 30 dogs), cyclosporine at a low dosage (2.5 mg/kg [1.1 mg/lb], PO, q 24 h; 30 dogs), or cyclosporine at a high dosage (5.0 mg/kg, PO, q 24 h; 31 dogs). Because cyclosporine was available only as a solution, dogs treated with cyclosporine at the low dosage were given 0.025 ml/kg (0.011 ml/lb) once daily, and dogs treated with cyclosporine at the high dosage were given 0.05 ml/kg (0.022 ml/lb) once daily. All treatments were given for 6 weeks at approximately the same time each day; treatments were administered at least 2 hours before or after dogs were fed.

Maintenance of blinding—Active and placebo solutions were dispensed in identical bottles with similar-looking labels. Because cyclosporine solution was available only at a concentration of 100 mg/ml, volumes administered to dogs in the low- and high-dosage groups were different. Therefore, all drugs were delivered to participating owners by a single individual who was not otherwise involved in the study.

Assessment of compliance by owner—Verification of each owner's compliance with the established protocol was assessed by reviewing daily records of drug administration and by measuring the amount of solution remaining after 6 weeks and comparing this amount with the amount expected on the basis of volume to be administered. In addition, a blood sample was collected from all dogs during the final examination, and blood cyclosporine concentration was measured with a commercial assay.^b All samples were analyzed by a single laboratory.^c

Clinicopathologic testing—To determine whether cyclosporine administration altered results of common clinicopathologic tests, blood samples were collected and submitted for hematologic and serum biochemical testing at the time of inclusion in the study and at the time of the final examination.

Primary and secondary outcome measures—Efficacy was assessed primarily by studying changes in scores for severity of skin lesions. Owner-recorded scores of severity of pruritus and scores of global efficacy were used as secondary measures of efficacy. All variables were assessed at the time of inclusion in the study (day 0) and during follow-up examinations on days 10, 21, and 42.

Skin lesion score—Severity of skin lesions associated with AD was assessed with a scoring system modified from the original canine atopic dermatitis extent and severity index (CADESI).²³ The revised CADESI consisted of an assessment of the severity (0 = no evidence, 1 = mild, 2 = moderate, and 3 = severe) of 3 different clinical signs of AD at 40 separate sites covering the body. Clinical signs evaluated included erythema (a marker of acute skin inflammation), lichenification (a sign of chronic cutaneous inflammation),

and excoriations (a sign of pruritus). The maximum CADESI score, therefore, was 360 (ie, $3 \times 3 \times 40$).

Preliminary analyses suggested that scores for the revised CADESI were associated with low variability for repeated assessments by a single clinician (mean coefficient of variation for 10 dogs with AD, 9%). The coefficient of variation was considered to reflect acceptable intra-assessor reliability over time. In addition, results of unpublished clinical trials involving dogs with AD suggested that a > 50% decrease in the CADESI score was highly correlated with an overall assessment of treatment efficacy by both owners and clinicians.⁴

Owner-assigned pruritus score—Every 7 days, owners estimated severity of pruritus during the preceding 3 days by drawing a mark on a 10-cm visual analog scale. The leftmost edge of the scale was labeled “your dog never scratches or bites itself, or only occasionally as any dog would”; the rightmost edge of the scale was labeled “your dog scratches and bites almost constantly and is in great discomfort.”

Global assessment of efficacy—At the end of treatment (ie, day 42), or earlier for dogs removed from the study, investigators and owners rated their perception of treatment efficacy as none, poor, fair, good, or excellent.

Statistical analyses—Because at least 1 follow-up evaluation was completed for all dogs, data from all study subjects were kept for intent-to-treat analyses. For dogs that did not complete the study, the imputation rule for missing data was the last-value-carry-forward rule.

All statistical analyses were performed with standard software.^{4,5} Efficacy of randomization was assessed by comparing demographic, historical, and clinical data among groups with 2-sided Fisher exact tests (categorical data) or by means of ANOVA (continuous data). For ANOVA, homogeneity of variance was evaluated with the Levene test. If the variance was not homogeneous, variables were transformed to achieve homogeneity. Efficacy of treatment was assessed by calculating the percentage reduction, compared with baseline (day 0) values of skin lesion (CADESI) and owner-assigned pruritus scores for each dog. Values were then compared among groups by use of repeated-measures ANOVA. Separate ANOVA, Dunnett tests, and Cochran-Mantel-Haenszel trend tests were performed to compare percentage reductions in skin lesion and pruritus scores among groups at each of the follow-up visits and to compare final investigator-assigned and owner-assigned global scores of efficacy.

The effect of co-variables that potentially could have influenced clinical responses was analyzed among groups. Whether dogs had a history of seasonal AD was determined to affect some of the outcome measures; therefore, effects of seasonality of AD on the main outcome variables (skin lesion, pruritus, and global assessment scores) and on subgroup comparisons were analyzed.

For all analyses, values of $P < 0.05$ were considered significant. Whenever possible, data are given as mean and 95% confidence interval (CI).

Results

Study participants—Ninety-one dogs with AD were enrolled in the study by 16 participating investigators. Subjects enrolled by each investigator were balanced among treatment groups, as all but 1 investigator enrolled 3 dogs or some multiple of 3 dogs in the study. Dogs included in the study represented > 30 breeds. The most common breeds of dogs were German Shepherd Dog (11 dogs), Labrador Retriever (8), Shih Tzu (7), and West Highland White Terrier (7).

Verification of the effectiveness of randomization—To determine whether randomization resulted in selection bias among groups, sex distribution, type of housing, type of diet fed, percentage of dogs with a history of seasonal AD, time since initial diagnosis of AD, age, body weight, skin lesion score, and pruritus score at the time of enrollment in the study were compared among groups. No significant differences were identified (Table 1). Dogs of the most common breeds were equally distributed among groups. In addition, no differences among groups were detected in regard to previous treatment with antimicrobials, antifungal drugs, glucocorticoids, allergen-specific immunotherapy, and antiparasitic medications.

Verification of owner compliance—Review of owner-maintained daily records of drug administration did not reveal any major deviations from the prescribed treatment. Volume of drug used deviated by > 20% from the theoretical volume prescribed for only 5 dogs in each group.

Dogs given the placebo all had blood cyclosporine concentrations less than the analytical limit of detection of the test (8 ng/ml). Blood cyclosporine concentrations for dogs in the 2 treatment groups were plotted against predicted values, determined from a population kinetic analysis involving laboratory dogs. Almost all measured concentrations were found to match concentrations predicted on the basis of the pharmacokinetic population analysis.

Withdrawal—Three dogs receiving the placebo and 1 dog receiving cyclosporine at the low dosage were withdrawn from the study because of inefficacy. The incidence of withdrawal was not significantly dif-

Table 1—Comparison of selected demographic variables among groups of dogs enrolled in a study to evaluate efficacy of cyclosporine, given at 1 of 2 dosage, in the treatment of atopic dermatitis (AD)

Variable	Placebo	Cyclosporine		P value
		Low dosage	High dosage	
Sex				0.30
Male	16	10	14	
Female	14	20	17	
Type of housing				0.37
Urban	19	14	14	
Rural	8	15	15	
Other	3	1	2	
Type of diet				0.09
Homemade	9	5	15	
Commercial	18	20	14	
Combination	3	5	2	
Seasonality of AD				0.95
No	21	20	22	
Yes	9	10	9	
Age (y)*	5.4 ± 2.5	5.6 ± 2.9	4.8 ± 3.0	0.54
Body weight (kg)*	19.5 ± 12.2	21.5 ± 12.6	21.6 ± 12.4	0.76
Skin lesion score*	63 ± 33	68 ± 28	63 ± 34	0.77
Pruritus score*	66 ± 19	74 ± 19	72 ± 24	0.26
Time since diagnosis of AD (mo)	39 ± 23	34 ± 24	33 ± 27	0.65

Categorical data are given as number of dogs; continuous data are given as mean ± SD. Fisher exact tests were used for categorical data; ANOVA was used for continuous data. Skin lesion scores were generated with the canine atopic dermatitis extent and severity index (maximum score, 360). Pruritus scores were assigned by the owners with a visual analog scale.

*At the onset of the study.

ferent among groups ($P = 0.123$). All 4 dogs were withdrawn shortly before or after examination on day 21. At the time of withdrawal, the skin lesion score had increased by 20 to 39%, compared with baseline values for these dogs. Data from these dogs were included in intent-to-treat analyses.

Skin lesion scores—During the course of the study, CADESI skin lesion scores decreased in dogs in all 3 groups, but the magnitude of the reduction in values was more rapid, steady, and profound in the high-dosage group (Fig 1). On days 10, 21, and 42, mean percentage reduction in skin lesion scores was significantly greater for dogs given cyclosporine at the high dosage than for dogs given the placebo, whereas mean percentage reduction in skin lesion scores for dogs given cyclosporine at the low dosage was not significantly different from the value for dogs given the placebo.

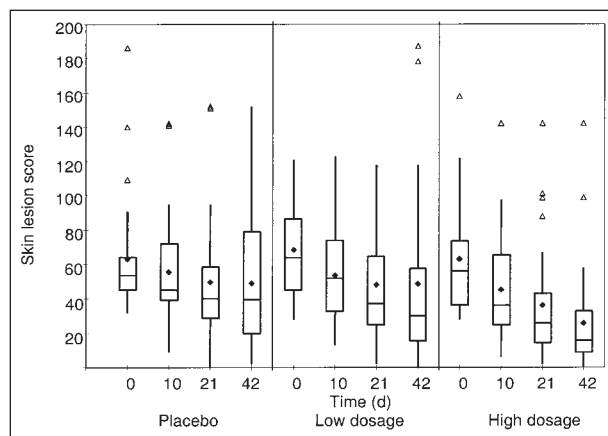


Figure 1—Box-and-whisker plots of skin lesion scores in dogs given a placebo or cyclosporine at a low or high dosage for treatment of atopic dermatitis (AD). The box represents the interquartile (25th to 75th percentiles) range. The horizontal line in the box represents the median. The whiskers represent the maximum and minimum values (with each whisker being no longer than 1.5 times the height of the box). Open triangles represent outliers. Closed diamonds represent the mean.

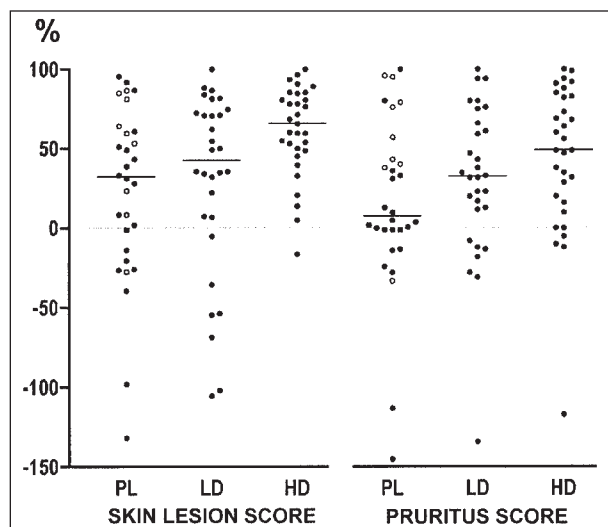


Figure 2—Percentage change after 6 weeks of treatment in skin lesion and pruritus scores for dogs with AD given a placebo (PL) or treated with cyclosporine at a low (LD) or high (HD) dosage.

bo. Mean percentage reductions in skin lesions scores at the end of the treatment period (day 42) were 34% (95% CI; 14 to 50%) for dogs given the placebo, 41% (23 to 57%) for dogs given cyclosporine at the low dosage, and 67% (53 to 78%) for dogs given cyclosporine at the high dosage (Fig 2).

The day-42 skin lesion score was improved by $\geq 50\%$, compared with baseline values, in 11 of the 30 (37%) dogs given the placebo, 14 of the 30 (47%) dogs given cyclosporine at the low dosage, and 22 of the 31 (71%) dogs given cyclosporine at the high dosage (Fig 2). Conversely, the day-42 skin lesion score was greater than the baseline score (ie, percentage reduction was negative) in 9 of the 30 (30%) dogs given the placebo, 7 of the 30 (23%) dogs given cyclosporine at the low dosage, and only 1 of the 31 (3%) dogs given cyclosporine at the high dosage. Values for dogs given cyclosporine at the high dosage were significantly ($P = 0.002$) different from values for dogs given cyclosporine at the low dosage and dogs given the placebo, but were not significantly different between dogs given cyclosporine at the low dosage and dogs given the placebo.

Owner-assigned pruritus scores—In all 3 groups, mean pruritus scores decreased progressively over time (Fig 3). On day 42, mean percentage reduction in pruritus score was significantly greater for dogs given cyclosporine at the high dosage than for dogs given the placebo, whereas mean percentage reduction in pruritus scores for dogs given cyclosporine at the low dosage were not significantly different from the value for dogs given the placebo. Mean percentage reductions in pruritus scores at the end of treatment period (day 42) were 15% (95% CI, -4 to 33%) for dogs given the placebo, 31% (12 to 49%) for dogs treated with cyclosporine at the low dosage, and 45% (27 to 63%) for dogs treated with cyclosporine at the high dosage (Fig 2).

The day-42 pruritus score was improved by $\geq 50\%$, compared with baseline values, in 7 of the 30 (23%) dogs given the placebo, 10 of the 30 (33%) dogs given cyclosporine at the low dosage, and 15 of the 31 (48%) dogs given cyclosporine at the high dosage (Fig 2).

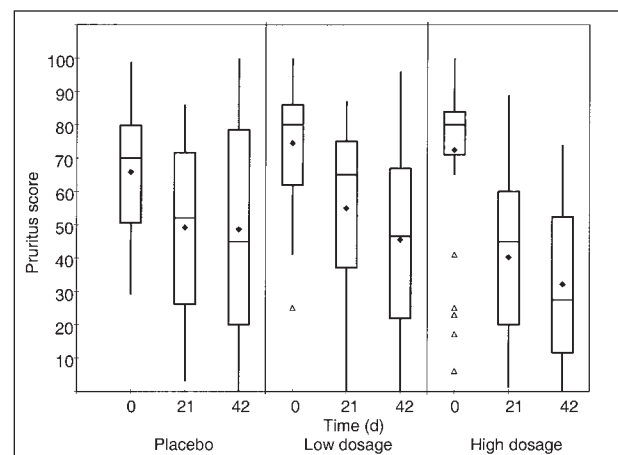


Figure 3—Box-and-whisker plots of owner-assigned pruritus scores in dogs given a placebo or cyclosporine at a low or high dosage for treatment of AD. See Figure 1 for key.

Conversely, the day-42 pruritus score was greater than the baseline score (ie, percentage reduction was negative) in 10 of the 30 (33%) dogs given the placebo, 7 of the 30 (23%) dogs given cyclosporine at the low dosage, and 4 of the 31 (13%) dogs given cyclosporine at the high dosage. Values for dogs given cyclosporine at the high dosage, but not for dogs given cyclosporine at the low dosage, were significantly different from values for dogs given the placebo.

Global assessments of efficacy—After 6 weeks of treatment (ie, day 42), investigators rated treatment efficacy as good or excellent for 9 of the 30 (30%) dogs given the placebo, 12 of the 30 (40%) dogs given cyclosporine at the low dosage, and 19 of the 31 (61%) dogs given cyclosporine at the high dosage. The percentage for dogs given cyclosporine at the high dosage was significantly ($P = 0.004$) greater than the percentage for dogs given the placebo, whereas the difference between dogs given cyclosporine at the low dosage and dogs given the placebo was not significant ($P = 0.318$).

Owner-assigned global assessments of treatment efficacy mirrored those recorded by the investigators. Efficacy was rated as good or excellent for 11 of the 30 (30%) dogs given the placebo, 10 of the 30 (40%) dogs given cyclosporine at the low dosage, and 19 of the 31 (61%) dogs given cyclosporine at the high dosage. The percentage for dogs given cyclosporine at the high dosage was significantly ($P = 0.014$) greater than the percentage for dogs given the placebo, whereas the difference between dogs given cyclosporine at the low dosage and dogs given the placebo was not significant ($P = 0.85$).

Effects of adjunctive treatment—Treatment of dogs with AD often necessitates use of adjunctive treatments such as antipruritic, anti-inflammatory, antimicrobial, or moisturizing shampoos or conditioners. During the course of the study, topical treatments other than those for control of fleas were used more frequently among dogs given the placebo than among dogs in the 2 other groups. Ten dogs given the placebo received antimicrobial drugs topically or orally, compared with 2 dogs given cyclosporine at the low dosage and 4 dogs given cyclosporine at the high dosage ($P = 0.04$). Antiseptic solutions were used in 2 dogs given the placebo, 1 dog given cyclosporine at the low dosage, and 1 dog given cyclosporine at the high dosage. Similarly, an ear cleaning solution was used in 2 dogs given the placebo, 3 dogs given cyclosporine at the low dosage, and 1 dog given cyclosporine at the high dosage. Finally, emollient, astringent, or soothing shampoos were used in 7 dogs given the placebo, 5 dogs given cyclosporine at the low dosage, and 3 dogs given cyclosporine at the high dosage.

Effect of seasonality of AD on skin lesion scores—Nine or 10 dogs in each group had a history of seasonal AD, and skin lesion scores decreased in most dogs with seasonal AD. Thus, for dogs with seasonal AD, mean percentage reduction in skin lesion scores on day 42 was not significantly different among groups (Table 2). Among dogs without a history of seasonal AD, mean percentage reduction in skin lesion scores

Table 2—Percentage reduction, compared with baseline (day 0) values, in skin lesion and owner-assigned pruritus scores at the end of a 6-week treatment period for dogs enrolled in a study evaluating efficacy of cyclosporine for the treatment of AD

Variable	Placebo	Cyclosporine	
		Low dosage	High dosage
Skin lesion score			
Dogs with seasonal AD	59 (36–77)	57 (34–75)	63 (41–80)
Dogs with nonseasonal AD	21 (–7–44)	32 (6–54)	69 (51–82)*
Pruritus score			
Dogs with seasonal AD	66 (30–83)	49 (26–73)	34 (9–58)†
Dogs with nonseasonal AD	–1 (–24–22)	20 (–3–45)	48 (27–71)*

Data are given as mean (95% confidence interval). Negative numbers indicate a worsening of scores, whereas positive numbers indicate an improvement.
 *Significantly ($P < 0.01$) different from value for dogs given the placebo.
 †Significantly ($P < 0.05$) different from value for dogs given the placebo.

on day 42 was significantly ($P < 0.01$) greater for dogs given cyclosporine at the high dosage than for dogs given the placebo. Values for dogs given cyclosporine at the low dosage were not significantly different from values for dogs given the placebo.

Effect of seasonality of AD on owner-assigned pruritus scores—Seasonality of AD also affected pruritus scores. For dogs with seasonal AD, mean percentage reduction in pruritus score on day 42 was significantly less for dogs given cyclosporine at the high dosage, compared with the value for dogs given the placebo (Table 2). Conversely, among dogs without a history of seasonal AD, mean percentage reduction in pruritus score on day 42 was significantly greater for dogs given cyclosporine at the high dosage than for dogs given the placebo.

Effect of seasonality of AD on global assessment scores—For dogs without a history of seasonal AD, efficacy of treatment was rated as good or excellent by the investigators for 4 of the 21 (19%) dogs given the placebo, 6 of the 20 (30%) dogs given cyclosporine at the low dosage, and 14 of the 22 dogs (64%) given cyclosporine at the high dosage. Percentages were significantly ($P < 0.001$) different between dogs given cyclosporine at the high dosage and dogs given the placebo but were not significantly ($P = 0.24$) different between dogs given cyclosporine at the low dosage and dogs given the placebo.

Similarly, for dogs without a history of seasonal AD, efficacy of treatment was rated as good or excellent by the owners of 5 of the 21 (24%) dogs given the placebo, 5 of the 20 (25%) dogs given cyclosporine at the low dosage, and 14 of the 22 dogs (64%) given cyclosporine at the high dosage. Percentages were significantly ($P = 0.004$) different between dogs given cyclosporine at the high dosage and dogs given the placebo but were not significantly ($P = 0.38$) different between dogs given cyclosporine at the low dosage and dogs given the placebo.

Among dogs with a history of seasonal AD, percentages of dogs for which treatment efficacy was rated as good or excellent by investigators and owners were not significantly different among groups (between 56 and 60% for each group).

Adverse drug effects—All adverse events, regardless of severity or duration and regardless of whether they were or were not suspected to be drug related, were recorded during the study. The frequency of reported adverse events was lower among dogs given the placebo (10/30 [33%] dogs; 19 events) than among dogs given cyclosporine at the low dosage (15/30 [50%] dogs; 27 events) and dogs given cyclosporine at the high dosage (18/30 [60%] dogs; 47 events). However, differences among groups were not significant. Most adverse events were rated as mild by the investigators. Severe adverse events were recorded twice among dogs given the placebo, once among dogs given cyclosporine at the low dosage, and 4 times among dogs given cyclosporine at the high dosage.

Emesis was the most common adverse event among dogs given the placebo (5 dogs [17%]) or cyclosporine at the low (10 dogs [33%]) or high (13 dogs [42%]) dosage. In all dogs, emesis occurred only once or intermittently. In no case was treatment interrupted because of the severity of vomiting.

Diarrhea was seen in 4 (13%) dogs given the placebo, 1 (3%) given cyclosporine at the low dosage, and 5 (16%) given cyclosporine at the high dosage. Similarly to emesis, diarrhea was generally of short duration (usually < 1 week). One dog given the placebo and 1 given cyclosporine at the high dosage had diarrhea for > 1 month.

Pyoderma or pyotraumatic dermatitis were diagnosed in 3 (10%) dogs given the placebo, 1 (3%) dog given cyclosporine at the low dosage, and 2 (6%) dogs given cyclosporine at the high dosage. These percentages were not significantly different among groups. During the study, *Malassezia* dermatitis was reported in 1 dog given the placebo. This diagnosis also was made incidentally in 1 dog given cyclosporine at the high dosage.

Effect on hematologic and serum biochemical test results—There was a slight increase in RBC count, hemoglobin concentration, and Hct among dogs receiving cyclosporine, compared with dogs receiving placebo, but differences were not statistically significant between groups. Similarly, there were no significant alterations in WBC count or in differential counts of neutrophils, basophils, lymphocytes, and monocytes among groups. A small (2.3%) but significant ($P = 0.033$) reduction in the percentage of circulating eosinophils was detected in dogs given cyclosporine at the high dosage, compared with dogs given cyclosporine at the low dosage and dogs given the placebo.

At the end of the study, significant variations from baseline values for serum creatinine and urea nitrogen concentrations were not seen in any of the groups. In all 3 groups, the mean percentage change in serum creatinine concentration was < 2.5%. Similarly, percentage changes, compared with baseline values, in serum urea nitrogen concentrations were 8% for dogs given the placebo, 16% for dogs given cyclosporine at the low dosage, and 10% for dogs given cyclosporine at the high dosage.

Percentage changes in alanine aminotransferase,

aspartate aminotransferase, and alkaline phosphatase activities, compared with baseline, were not significantly different among groups.

Discussion

Results of the present study suggest that oral administration of cyclosporine at a dosage of 5.0 mg/kg once daily is effective in reducing severity of pruritus and skin lesions in dogs with AD, especially those with nonseasonal disease. On the other hand, administration at a dosage of 2.5 mg/kg once daily was not significantly more efficacious than administration of a placebo.

During the 6-week course of this study, mean and median skin lesion and pruritus scores progressively decreased in all 3 study groups, even the group receiving the placebo. However, percentage changes from baseline values for skin lesion and pruritus scores were highest for dogs given cyclosporine at the high dosage, and only for dogs given cyclosporine at the high dosage, were percentage reductions in scores significantly different from values for dogs given the placebo. Additionally, the frequency of administration of concomitant antimicrobial medications was lower among dogs given cyclosporine at the high dosage, compared with dogs given the placebo.

The magnitude of improvement in skin lesion and pruritus scores among dogs given a placebo in the present study was remarkable. However, a noticeable placebo effect was also reported in 2 previous randomized controlled trials^{24,25} investigating the efficacy of antiallergic drugs in dogs with AD. In the present study, subgroup analyses comparing reductions in severity of clinical signs in dogs with or without a history of seasonal AD provided a logical explanation for the improvement in skin lesion and pruritus scores among dogs given the placebo. When analyses were restricted to dogs with a history of seasonal disease, the reduction in owner-assigned pruritus scores was highest for dogs given the placebo and lowest for dogs given cyclosporine at the high dosage. In contrast, when analyses were restricted to dogs without a history of seasonal disease, the improvement in dogs given the placebo was minimal. Thus, these subgroup analyses suggest that the improvement among dogs given the placebo in the present study likely was a result of a change in season, a surprising fact in light of the short duration of this study. Moreover, our findings justify the use of a placebo group and limiting enrollment to dogs with nonseasonal AD in future clinical trials investigating the efficacy of antiallergic drugs in dogs with AD.

In this study, quantitative skin lesion scores, derived from the CADESI, were used to evaluate changes in extent and severity of skin lesions associated with AD. Criteria and methods used to generate these scores were similar to those used for the PASI²⁶ and the SCORAD index,^{27,28} 2 standard scoring methods used in clinical trials of human patients with psoriasis and AD, respectively. We believe that the CADESI represents a reliable and relevant method of assessing severity of clinical signs of AD in dogs. Indeed, in

the present study, the percentage reduction compared with baseline values in skin lesion scores was found to be significantly correlated with the overall clinical evaluation given by the investigators ($r = 0.73$; $P = 0.03$).

Few randomized controlled trials evaluating pharmacologic management of AD have been conducted on large populations of dogs. Moreover, quantitative criteria to assess response to treatment generally were not used in these early trials. Such imprecision unfortunately prevents a reliable comparison of clinical responses between trials. Nevertheless, the clinical improvement obtained with cyclosporine at the high dosage in the present study appeared to be better than that reported in open clinical trials of antihistamines, in which partial clinical improvement in up to 30% of the patients could be seen.²⁹ Moreover, 2 randomized clinical trials^{30,31} failed to reveal any efficacy of 2 antihistamines. Similarly, randomized controlled trials of the efficacy of essential fatty acids supplements report inconstant improvement.³² On the other hand, efficacy of cyclosporine at the high dosage in the present study was of similar magnitude to that associated with glucocorticoids.³³

Randomized controlled trials^{12,34} similar to the present study have been performed with human patients with AD. In these studies, the magnitude of improvement in disease extent and severity during a 6-week period was similar to that found in the present study. Moreover, in 1 study¹³ involving human patients, administration of cyclosporine at a dosage similar to that used in the present study resulted in a similar rate of excellent or good responses as seen in our trial. In contrast, unlike results of the present study, the response to administration of cyclosporine at a dosage of 2.2 mg/kg (1 mg/lb) once daily in human patients is still good and only slightly inferior to administration at a dosage of 4.2 mg/kg (1.9 mg/lb) once daily. A high dosage is required only for human patients with severe pruritus.¹³ Finally, the improvement in quality of life correlated only partially with clinical amelioration in a clinical trial of human patients with AD.¹¹ Unfortunately, this aspect was not specifically evaluated in our work.

In the present study, adverse drug events—usually vomiting and diarrhea—were seen commonly in dogs of all 3 groups. However, the incidence of these adverse events was not significantly different among groups, and in most instances such events were considered mild. Six dogs, in addition to those withdrawn for inefficacy, developed a bacterial or yeast skin infection that necessitated cessation of treatment. However, these 6 dogs were removed from the study because of study exclusion criteria and not because of profound alterations in quality of life.

Clinically important changes in results of hematologic or serum biochemical tests among dogs receiving cyclosporine were not identified in the present trial, and the safety of cyclosporine administration has been documented in a previously published paper.³⁵ In that report,³⁵ 32 Beagles were administered vehicle or cyclosporine at a dosage of 5, 15, or 45 mg/kg/d for 1 year. At the end of the study, dogs given cyclosporine at a dosage of 45 mg/kg/d (9 times the dosage used

herein) did not have any indications of hepatotoxic, nephrotoxic, or myelotoxic effects. However, vomiting and diarrhea were common among dogs receiving cyclosporine at dosages of 15 and 45 mg/kg/d and led to weight loss. Hematologic and biochemical changes in dogs given cyclosporine at a dosage of 45 mg/kg/d included anemia, leukopenia, hypoalbuminemia, and hyperglobulinemia.

The present study was designed as a randomized controlled trial involving 91 dogs with AD in which concurrent and complicating diseases had been ruled out. Efficacy was considered to be good or excellent by owners and investigators for 61% of the dogs treated with cyclosporine at a dosage of 5.0 mg/kg once daily. Moreover, a > 50% reduction, compared with baseline values, in skin lesion and pruritus scores was seen for 71 and 48%, respectively, of the dogs in this group. We believe that because of the study's design, inclusion and exclusion criteria, and outcome measures, the results provide clinically relevant information that can be extrapolated when veterinary practitioners treat dogs with AD. Results of this trial, in combination with results of an open pilot study¹⁷ and results of a previous randomized controlled trial,¹⁸ provide good evidence to support the recommendation that cyclosporine, at a dosage of 5.0 mg/kg, PO, every 24 hours, can be used for treatment of dogs with AD.

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^aNEORAL, Novartis-Pharma, Basel, Switzerland.

^bTDx/TDxFLx Cyclosporine monoclonal whole blood assay, Abbott Diagnostics, Baar, Switzerland.

^cNovartis Animal Health Research Center, St Aubin, Switzerland.

^dNovartis Animal Health; data on file.

^eSAS Version 6.12, SAS Institute, Cary, NC.

^fS-PLUS, MathSoft Inc, Seattle, Wash.

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