

Clinical trial evaluating the efficacy and safety of cyclosporine in dogs with atopic dermatitis

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Objective—To determine efficacy and safety of cyclosporine in the treatment of atopic dermatitis among dogs in North America.

Design—Randomized controlled (phase 1) and open-label (phase 2) trials.

Animals—268 dogs with atopic dermatitis.

Procedure—In phase 1, dogs were randomly assigned to be treated with cyclosporine (5 mg/kg [2.3 mg/lb], PO, q 24 h) or a placebo. In phase 2, all dogs were treated with cyclosporine for 16 weeks. Frequency of cyclosporine administration was decreased if dogs improved clinically.

Results—At the end of phase 1, canine atopic dermatitis extent and severity index (CADESI) scores for dogs treated with cyclosporine were significantly lower than scores for control dogs. Percentage of dogs with severe pruritus decreased from 67% to 16% for the cyclosporine group but from 66% to only 61% for the control group. During phase 2, cyclosporine dosage was decreased to every-other-day administration in 39% of the dogs after 4 weeks. After 12 weeks, 22% of the dogs were treated twice weekly and 36% were treated every other day. After 16 weeks, CADESI score had decreased > 50% in 68% of the dogs and 47% of dogs had no or mild pruritus. The most frequent adverse reactions were gastrointestinal tract signs.

Conclusions and Clinical Relevance—Results suggest that cyclosporine is efficacious for the treatment of atopic dermatitis in dogs and that frequency of cyclosporine administration can be reduced following an initial induction period. The drug was well tolerated. (*J Am Vet Med Assoc* 2005;226:1855–1863)

Several studies^{1-5,a} have shown that cyclosporine is efficacious in the treatment of dogs with atopic dermatitis. For instance, in a randomized controlled trial² comparing 2 dosages of cyclosporine (2.5 mg/kg [1.1 mg/lb] and 5 mg/kg [2.3 mg/lb], PO, q 24 h), treatment with cyclosporine at the higher dosage resulted in significant improvements in clinical signs, compared with a placebo treatment. In a separate study,³ cyclosporine

was found to be as effective as prednisolone in controlling skin lesions and pruritus, and in a randomized controlled trial in Europe,⁴ a microemulsion formulation of cyclosporine was found to be comparable to methylprednisolone in controlling skin lesions and pruritus. In a follow-up to the latter study,⁵ the relapse rate was lower and clinical signs were less severe during the 2 months after treatment was discontinued in dogs that had been treated with cyclosporine, compared with dogs that had been treated with methylprednisolone. However, all of these previous studies were performed in Europe, and it is not clear whether results can be generalized to dogs in North America because of differences in climate, allergen exposure, and environmental conditions.

Results of these previous studies^{1-5,a} have suggested that cyclosporine is safe in dogs, with the most common adverse effects being gastrointestinal tract abnormalities during the first 2 weeks of treatment. The frequency of bacterial and yeast infections did not increase during treatment with cyclosporine, and no impairment of renal function was identified in any of these studies. However, treatment was generally of short duration in these studies, which may not reflect clinical use in dogs with the disease. Thus, the safety of long-term use of cyclosporine in dogs is still unclear.

The purposes of the study reported here, therefore, were to determine efficacy of cyclosporine for treatment of recurrent atopic dermatitis among dogs in North America and to evaluate safety of the drug when administered for 4 months.

Materials and Methods

Study design—The study was performed in 2 phases. Phase 1 consisted of a randomized controlled trial in which dogs were randomly assigned to be treated with cyclosporine or a placebo for 4 weeks. Dogs that completed phase 1 were enrolled in phase 2, which was conducted as an open-label trial during which all dogs received cyclosporine. During phase 2, dogs that received cyclosporine during phase 1 were treated with cyclosporine for an additional 3 months and dogs that received the placebo during phase 1 were treated with cyclosporine for 4 months.

The study was conducted in compliance with the Veterinary International Committee for Harmonization guideline 9 for good clinical practice. Seventeen study sites participated. All 17 study sites were referral-based, nonacademic, specialty practices, and all but 1 investigator were diplomates of the American College of Veterinary Dermatology or residents in veterinary dermatology. Fifteen of the study sites were located in the United States (Texas, Florida, California, Ohio, New York, Colorado, Washington, Arizona, New Jersey, North Carolina, and Georgia), and 2 were located in Ontario, Canada. Each study site enrolled between 7 and 33 patients.

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Inclusion and exclusion criteria—Client-owned dogs in which atopic dermatitis had been diagnosed were eligible for inclusion in the study. To be included in the study, dogs had to be at least 1 year old with a history of nonseasonal, chronic or recurrent dermatitis for at least 1 year and be free from fleas or be receiving a long-acting flea adulticide at the time of enrollment. Cutaneous adverse food reactions, flea-bite hypersensitivity, and ectoparasite infections had to have been ruled out by means of standard diagnostic or therapeutic methods, and the diagnosis of atopic dermatitis had to have been made on the basis of standard criteria.^{6,7} Additionally, during the 6 months prior to enrollment, dogs must have undergone intradermal testing and had immediate positive responses to environmental allergens such as house dust mite, pollens, or molds or have been found to have high serum concentrations of allergen-specific IgE. Dogs with bacterial skin infections were eligible for inclusion in the study only after treatment with antimicrobials for at least 4 weeks; dogs with fungal skin infections were eligible for inclusion in the study only after treatment with antifungal agents for at least 3 weeks.

So that meaningful improvements in clinical signs could be detected during the study, dogs were eligible for inclusion only if they had a baseline **canine atopic dermatitis extent and severity index (CADESI)** score ≥ 25 . Scores were assigned by participating investigators as described.² Briefly, the severity (0 = no evidence, 1 = mild, 2 = moderate, and 3 = severe) of 3 clinical signs (erythema, excoriations, and lichenification) of atopic dermatitis was assessed at 40 sites on the body. The maximum CADESI score, therefore, was 360 ($3 \times 3 \times 40$).

Dogs were excluded from the study if disease history and results of diagnostic testing and previous treatment were not clearly documented, the dog was pregnant or lactating, the dog had a medical condition that could interfere with the evaluation of treatment outcome, or the dog had a skin infection that required long-term antimicrobial or antifungal treatment. Dogs with concurrent uncontrolled adverse food reactions or uncontrolled flea allergy dermatitis were also excluded from the study.

A washout period of 2 weeks was required for dogs that had been treated with corticosteroids PO, and a washout period of 8 weeks was required for dogs that had been treated with long-acting glucocorticoids by injection. In addition, allergen-specific immunotherapy could not have been initiated in the 2 weeks preceding enrollment, and treatment with any drug known to interfere with the pharmacokinetics of cyclosporine (eg, ketoconazole) had to be discontinued prior to enrollment. However, dogs that were receiving nonpharmaceutical treatments (eg, a hypoallergenic diet, oatmeal baths, or brewer's yeast) were not excluded from the study, and owners were allowed to continue these treatments during the study.

Owners of dogs considered for inclusion received detailed information on the study and provided written informed consent before their dogs were enrolled. Owners were allowed to withdraw their dogs from the study at any time.

Sample size estimation—Calculations based on results of previous studies^{2,4} indicated that 50 dogs would be required to demonstrate a significant ($P < 0.05$) difference of at least 15% in CADESI scores with an 80% probability following treatment with cyclosporine or a placebo for 4 weeks. However, a larger population was enrolled so that safety of cyclosporine could be assessed during the open-label phase of the study.

Phase 1—The first phase of the study was conducted as a randomized controlled trial. Dogs enrolled in the study

were randomly assigned to the treatment or control group by use of standard software.^b Randomization was performed independently at each study site.

At each study site, participating investigators were responsible for medical evaluation of dogs and diagnosis of atopic dermatitis. A single individual at each site (usually a veterinary technician) was responsible for assigning dogs to treatment groups, handling test medications, ensuring proper dosing, and maintaining blinding. Cyclosporine^c used in the study was supplied as a promicroemulsion in soft gelatin capsules containing 10, 25, 50, or 100 mg of cyclosporine. The placebo consisted of identical soft gelatin capsules containing soybean oil.

Dogs assigned to the treatment group were treated with cyclosporine at a dosage of 3.3 to 6.6 mg/kg (1.5 to 3 mg/lb; mean, 5 mg/kg), PO, every 24 hours for 4 weeks. The proper dose was achieved with a single capsule or, at most, a combination of 2 capsules. Capsules were to be administered at least 2 hours before or after feeding.

To eliminate possible confounding associated with flea-bite dermatitis, an approved flea adulticide was applied to all dogs at the time of enrollment in the study (except for dogs examined at study sites located in areas free from fleas). Medical treatment was allowed for conditions not related to atopic dermatitis. All other medications (eg, anti-inflammatory drugs, antihistamines, and antimicrobials), including medications known to interfere with the pharmacokinetics of cyclosporine (eg, ketoconazole and itraconazole), were prohibited. Nonmedicated shampoos that were used regularly prior to enrollment in the study were allowed to be used at the same frequency.

Pet owners used treatment diaries to record drug administration throughout the study and were directed to return unused capsules to the individual responsible for maintaining blinding. Treatment compliance was assessed through the use of these owner-completed treatment diaries and counts of unused capsules. A blood sample was collected at the end of the 4-week treatment period, and serum cyclosporine concentration was measured with a commercial kit^d by a contract laboratory.^e

Dogs were evaluated prior to the initiation of treatment and at the end of the 4-week treatment period. At each evaluation, a CADESI score and an alopecia score were assigned by the investigator. For the alopecia score, severity of alopecia in 4 areas (head and neck, forelimbs, hind limbs, and ventral aspect of the thorax and abdomen) on both sides of the body was scored on a scale from 1 to 4 (1 = 0% to 25% hair loss, 2 = 26% to 50% hair loss, 3 = 51% to 75% hair loss, and 4 = 76% to 100% hair loss). Possible alopecia scores ranged from 8 (no or minimal hair loss) to 32 (complete alopecia).

At the same evaluation times, owners were asked to indicate severity of pruritus for their dogs on a scale from 1 to 5 (1 = dog does not scratch itself or just scratches from time to time like any dog would; 2 = dog scratches, bites, licks, or rubs itself occasionally, but the situation is tolerable, and the dog remains calm; 3 = dog scratches, bites, licks, or rubs itself, but the situation is generally tolerable; 4 = dog scratches, bites, licks, or rubs itself often and is often agitated; and 5 = dog scratches, bites, licks, or rubs itself constantly). At the end of the 4-week evaluation period, owners and investigators were asked to indicate how dogs had responded to treatment, compared with the dogs' condition at the time of enrollment in the study. Response options were poor, reasonable, good, excellent, and don't know.

Phase 2—Phase 2 of the study was performed as an open-label trial. Dogs that completed phase 1 were eligible for enrollment in phase 2. Dogs that had received the placebo during phase 1 were treated with cyclosporine for 16 weeks and reevaluated every 4 weeks. For the initial 4 weeks, the

dosage of cyclosporine was 5 mg/kg, PO, every 24 hours. Dogs were reevaluated after these initial 4 weeks, and severity of skin lesions and pruritus was assessed. The cyclosporine dosage was decreased to 5 mg/kg, PO, every 48 hours in dogs in which owner-assigned pruritus score had improved and CADESI score had decreased by > 50%. If the improvement in clinical signs was not maintained at the time of the next reevaluation 4 weeks later, the dosage was again increased to daily administration. If clinical signs were unchanged, the dosage was maintained as before. If the CADESI score had decreased by > 75%, compared with baseline score, without any change in owner-assigned pruritus score, the dosage was decreased to 5 mg/kg, PO, twice a week. At the time of the next reevaluation, the dosage was maintained as before if clinical signs were unchanged. If clinical signs were worse, the dosage was increased to 5 mg/kg, PO, every 48 hours.

Dogs enrolled in phase 2 that had received cyclosporine during phase 1 were treated with cyclosporine for an additional 12 weeks during phase 2. These dogs were reevaluated every 4 weeks, and the cyclosporine dosage was adjusted as described for the dogs that had received the placebo.

As during phase 1, treatment compliance was assessed every 4 weeks through the use of owner-completed treatment diaries and counts of unused capsules. Blood samples were collected after 4 weeks and assayed for cyclosporine concentration to confirm the drug was being administered.

Flea adulticide treatment was maintained throughout the study period. During phase 2, carefully controlled treatment of conditions related to atopic dermatitis, such as otitis, bacterial and fungal infections, and pododermatitis, was allowed. Duration of antimicrobial administration was limited to 10 days, and ketoconazole administration was restricted to a maximum of two 7-day courses of treatment. Use of corticosteroids and antihistamines was prohibited. The diet and dog's environment remained constant throughout phase 2. Shampoo use was allowed so long as the same product and use pattern was applied before and throughout the study.

To assess effects of cyclosporine on hematologic and serum biochemical variables, blood samples were collected for a CBC and serum biochemical profile at the time of enrollment in the study and after administration of cyclosporine for 8 and 16 weeks. Urine samples were collected at the time of enrollment in the study and after administration of cyclosporine for 8 and 16 weeks (or at the time of the last evaluation for dogs that did not complete the entire study).

At the time of each evaluation, CADESI, owner-assigned pruritus, and alopecia scores were obtained. In addition, investigators were asked to provide a global assessment (poor, reasonable, good, excellent, or don't know) of treatment response at the end of the study.

Statistical analyses—Data were analyzed on an intent-to-treat and per protocol basis. Data for all dogs that were reevaluated at least once were included in intent-to-treat analyses. For dogs that did not complete all of phase 2 of the study, the last-observed-value-carried-forward imputation rule was used for missing data. For per protocol analyses, dogs not in compliance with the treatment protocol were excluded after the deviation from the protocol occurred.

All statistical analyses were performed with standard software.^b Randomization effectiveness was verified by comparing demographic, historical, and clinical data between the treatment and control groups with the Mann-Whitney *U* test. The percentage reduction from baseline for CADESI and owner-assigned pruritus scores was calculated for each dog, and values were compared between groups with the Mann-Whitney *U* test. The same test was used to compare global assessments of treatment effectiveness between groups.

Wilcoxon pairwise analysis was used to compare CADESI, pruritus, and alopecia scores and hematologic and biochemical parameters with baseline values. Correlations between variables were assessed with the Spearman rank correlation test.

Dogs were stratified on the basis of body weight (< 15 kg, 15 to 29 kg [33 to 64 lb], and > 29 kg) to determine whether body weight had any effect on outcome. For each stratum, differences from baseline values were analyzed by use of Wilcoxon pairwise analyses.

For all analyses, values of $P < 0.05$ were considered significant. When appropriate, data are given as mean $\pm$ SD.

Results

Phase 1—A total of 268 dogs were enrolled in phase 1 of the study, with 134 assigned to the treatment group and 134 assigned to the control group. However, 6 dogs were not returned for reevaluation 4 weeks later. Therefore, intent-to-treat analyses were performed on data for 262 dogs (130 in the treatment group and 132 in the control group). A baseline CADESI score was not recorded for 1 dog; however, this dog was retained in the intent-to-treat analyses. Fifty dogs (27 in the treatment group and 23 in the placebo group) were excluded from per protocol analyses because prohibited concomitant treatments were administered during the study period, a re-evaluation was not performed 4 weeks after study enrollment, the wrong dosage of cyclosporine was administered, or the dog was withdrawn from the study by the owner or for various miscellaneous reasons. Thus, data for 218 dogs were included in per protocol analyses (107 in the treatment group and 111 in the control group).

Dogs in the study population represented 55 breeds. The most common breeds included Labrador Retrievers (72 dogs) and Golden Retrievers (72), followed by West Highland White Terriers (10) and German Shepherd Dogs (10). Remaining breeds were represented by fewer than 7 dogs. There were 45 mixed-breed dogs enrolled in the study.

No significant differences were found between the groups with respect to body weight, age distribution, breed distribution, or disease severity (Table 1). Dogs ranged from 14 months to 12.5 years old. The proportion of males in the cyclosporine group was significantly ($P = 0.05$) higher than the proportion of males in the control group.

Regardless of whether data were analyzed on an intent-to-treat or per protocol basis, mean CADESI score for dogs in the cyclosporine group was significantly ($P < 0.001$) lower than mean CADESI score for dogs in the control group at the end of phase 1 (Table 2). For dogs in the cyclosporine group, mean CADESI score at the end of phase 1 was significantly ($P < 0.001$) less than mean baseline score, whereas no significant difference was found for dogs in the control group.

At the end of phase 1, CADESI score had decreased, compared with baseline score, by $\geq 50\%$ in 58 of the 129 (45%) dogs in the cyclosporine group and 9 of the 132 (7%) dogs in the control group. Conversely, CADESI score increased in 10 of the 129 (7.8%) dogs in the cyclosporine group and 70 of the 132 (53%) dogs in the control group.

After 4 weeks of treatment, mean owner-assigned pruritus score was significantly ($P < 0.001$) decreased,

Table 1—Baseline characteristics of dogs enrolled in a randomized controlled trial of the efficacy of cyclosporine in the treatment of atopic dermatitis in dogs.

Variable	Cyclosporine group	Control group	P value
Sex distribution (male/female)	74/60	57/77	0.05
Weight (kg)*	25.4 ± 12.8	23.5 ± 13.9	0.20
Age distribution			0.09
1–5 years	73	60	
> 5–10 years	54	63	
> 10 years	7	11	
CADESI score*†	79.0 ± 51	79.2 ± 47	0.72
Pruritus score*‡	3.75 ± 1.06	3.68 ± 1.13	0.72
Alopecia score*§	14.6 ± 5.1	14.4 ± 5.2	0.71

CADESI = Canine atopic dermatitis extent and severity index.

*Values are given as mean ± SD. †Scores were assigned by assessing severity (0 = no evidence, 1 = mild, 2 = moderate, and 3 = severe) of 3 clinical signs (erythema, excoriations, and lichenification) of atopic dermatitis at 40 body sites (maximum score, 360). ‡Severity of pruritus was scored on a scale from 1 (dog does not scratch) to 5 (dog scratches constantly). §Severity of alopecia in 4 areas (head and neck, forelimbs, hind limbs, and ventral aspect of the thorax and abdomen) on both sides of the body was scored on a scale from 1 to 4 (1 = 0% to 25% hair loss, 2 = 26% to 50% hair loss, 3 = 51% to 75% hair loss, and 4 = 76% to 100% hair loss); possible score ranged from 8 to 32.

Table 2—Clinical signs in dogs with atopic dermatitis before and after treatment with cyclosporine for 4 weeks (5 mg/kg [2.3 mg/lb], PO, q 24 h) and in control dogs treated with a placebo.

Variable	Intent-to-treat analyses		Per protocol analyses	
	Cyclosporine (n = 130)	Control (132)	Cyclosporine (107)	Control (111)
CADESI score*				
Baseline	79.0 ± 51.0	79.2 ± 46.8	77.4 ± 50.5	74.8 ± 41.5
4 weeks	47.5 ± 43.6	84.3 ± 54.7	43.0 ± 38.0	81.3 ± 49.3
Pruritus score				
Baseline	3.75 ± 1.06	3.68 ± 1.13	3.75 ± 1.05	3.61 ± 1.13
4 weeks	2.39 ± 1.14	3.64 ± 1.11	2.28 ± 1.05	3.61 ± 1.10
Alopecia score				
Baseline	14.6 ± 5.1	14.4 ± 5.2	14.5 ± 5.1	14.0 ± 5.0
4 weeks	11.5 ± 5.4	14.6 ± 5.7	10.9 ± 5.0	14.3 ± 5.5

Data are given as mean ± SD. Intent-to-treat analyses included data for all dogs that were reevaluated. Per protocol analyses included data only for those dogs in compliance with the treatment protocol. For all 3 variables, values for dogs treated with cyclosporine were significantly ($P < 0.001$) different from values for control dogs at 4 weeks.

*Baseline CADESI score was missing for 1 dog in the cyclosporine group in the intent-to-treat analysis. See Table 1 for remainder of key.

compared with baseline score, among dogs in the cyclosporine group but not among dogs in the control group. In addition, mean score for dogs in the cyclosporine group at the end of phase 1 was significantly ($P < 0.001$) lower than mean score for dogs in the control group. At the time of enrollment, pruritus severity was assigned a score of 4 or 5 for 87 of the 130 (67%) dogs in the cyclosporine group and 87 of the 132 (66%) dogs in the control group. After 4 weeks, only 21 of 130 (16%) dogs in the cyclosporine group were assigned pruritus severity scores of 4 or 5, compared with 81 of 132 (61%) dogs in the control group.

The extent of alopecia was highly variable in the study population, with 73 and 85 dogs in the cyclosporine and control groups, respectively, reporting a score higher than the minimum score. After 4 weeks of treatment, mean alopecia score was significantly ($P < 0.001$) decreased, compared with baseline score, among dogs in the cyclosporine group but not among dogs in the control group (Table 2), and scores at the end of phase 1 were significantly ($P < 0.001$) different between groups. For dogs in the cyclosporine group, alopecia score improved by > 8 points in 4 of 73 (5%) dogs, improved by 3 to 8 points in 30 of 73 (41%) dogs, and improved by < 3 points or was unchanged in

39 of 73 (53%) dogs. By comparison, alopecia score improved by > 8 points in only 1 of 85 (1%) dogs in the control group, improved by 3 to 8 points in 15 of 85 (18%) dogs, and worsened in 69 of 85 (81%) dogs.

At the end of phase 1, investigators assessed overall response to treatment as excellent or good in 53% (intent-to-treat analysis) and 58% (per protocol analysis) of the dogs (Table 3). In contrast, investigators assessed overall response to treatment as excellent or good in only 6% and 5% of dogs in the control group. Global assessments were significantly ($P < 0.001$) different between groups.

When dogs were stratified according to body weight, changes in CADESI, owner-assigned pruritus, and alopecia scores (compared with baseline values) were not significantly different among the 3 body weight subgroups in either the cyclosporine or control group. Values were significantly ($P < 0.001$) different from baseline values for all 3 subgroups of the cyclosporine group.

For dogs in the cyclosporine group, no significant correlation was found between baseline CADESI score and percentage improvement in score after 4 weeks of treatment with cyclosporine. Global assessments of efficacy were also not significantly correlated with baseline CADESI ($P = 0.69$) or owner-assigned pruritus ($P = 0.85$) score.

Table 3—Global assessment of the response to treatment, as determined by the investigators, in dogs with atopic dermatitis treated with cyclosporine for 4 weeks or with a placebo.

Assessment	Intent-to-treat analysis		Per protocol analysis	
	Cyclosporine (n = 130)	Control (132)	Cyclosporine (107)	Control (111)
Poor	28 (22)	104 (79)	18 (17)	90 (81)
Reasonable	29 (22)	18 (14)	25 (23)	14 (13)
Good	39 (30)	6 (5)	32 (30)	4 (4)
Excellent	30 (23)	1 (1)	30 (28)	1 (1)
No response	4 (3)	3 (2)	2 (2)	2 (2)

Values are given as number of dogs (%). The distribution of outcomes was significantly ($P < 0.001$) different between groups.
See Tables 1 and 2 for key.

However, for all dogs in phase 1, the global assessment of efficacy was significantly correlated with percentage change in CADESI score ($P < 0.001$; $R = 0.72$) and with the difference in owner-assigned pruritus score from baseline ($P < 0.001$; $R = 0.68$). In 163 of the 178 (92%) dogs in which treatment response was considered poor or reasonable by the investigator, the CADESI score improved by $< 50\%$. Similarly, the pruritus score decreased by < 2 units in 167 of these 178 (94%) dogs. Conversely, the response was judged excellent or good in 47 of the 76 (62%) dogs in which CADESI score improved $> 50\%$ and in 49 of the 76 (64%) dogs in which pruritus score decreased by > 1 unit.

When the range of cyclosporine dosages (3.3 to 6.6 mg/kg) was examined, no correlation was identified between dosage and percentage change in CADESI score ($P = 0.76$; $R = 0.06$) or between dosage and difference in pruritus score from baseline ($P = 0.33$; $R = 0.1$).

Phase 2—Of the 266 dogs for which data were available, 78 dropped out of phase 2 of the study or were excluded. Reasons for dropout or exclusion were adverse reactions (11 dogs); recurrent pruritus, erythema, or otitis externa necessitating additional treatment (3); lack of improvement or deterioration of skin lesions or pruritus after 4 weeks of treatment (26); and miscellaneous other reasons (38). For per protocol analyses, most dogs were excluded because follow-up evaluations were missed by > 7 days, persistent errors in adjustments to the cyclosporine dosage, or the use of prohibited concomitant treatments. Data for most dogs in which doses were missed (usually single doses) were retained unless the owners discontinued administering cyclosporine or there was a flagrant disregard for the treatment plan.

Taking these dropouts into consideration, the number of dogs enrolled in the study decreased from 266 at the time of enrollment to 254, 239, 194, and 186 after 4, 8, 12, and 16 weeks, respectively, of treatment with cyclosporine. For per protocol analyses, numbers of dogs included decreased from 215 at the time of enrollment to 215, 179, 118, and 90 after 4, 8, 12, and 16 weeks, respectively, of treatment with cyclosporine.

According to owner-completed treatment diaries, owners forgot to administer occasional capsules of cyclosporine, but long periods without medication were rare. Treatment diaries and counts of unused capsules revealed good compliance with the treatment plan. Incidence of substantial underdosing was low; no overdosing was reported. Assays of serum cyclosporine

concentrations revealed that 10 of 248 dogs had concentrations less than the level of detection.

At each of the evaluation periods (ie, 4, 8, 12, and 16 weeks after initiation of cyclosporine treatment), median CADESI score was significantly ($P < 0.001$) less than baseline score (Figure 1). Visual inspection of scores indicated that approximately half the decrease in scores occurred during the first 4 weeks of cyclosporine administration, followed by a more gradual decrease over the subsequent 12 weeks.

On the basis of intent-to-treat analyses, CADESI score had decreased $> 50\%$, compared with baseline score, in 45%, 68%, 64%, and 68% of the dogs after 4, 8, 12, and 16 weeks, respectively, of cyclosporine treatment. On the basis of per protocol analyses, corresponding percentages with a $> 50\%$ decrease in CADESI score were 50%, 75%, 77%, and 87%, respectively. After 16 weeks of treatment with cyclosporine, 38% (intent-to-treat analysis) and 53% (per protocol analysis) had a $\geq 75\%$ decrease in CADESI score.

In the intent-to-treat analysis, the percentage of dogs with CADESI score > 70 decreased from 44% at the time of enrollment to 4% at the end of the study. Additionally, 62% of the dogs had scores ≤ 30 at the end of the study.

Mean $\pm$ SD owner-assigned pruritus score decreased from 3.71 ± 1.09 at the time of enrollment to 2.26 ± 1.14 (intent-to-treat analysis) and 1.96 ± 0.96 (per protocol analysis) at the end of the study. In the intent-to-treat analysis, the percentage of dogs with severe pruritus (score of 4 or 5) decreased from 64% (170/266 dogs) to 15% (40/266; Figure 2), whereas the percentage of dogs with no or mild pruritus (score of 1 or 2) increased from 12% (32/266) to 47% (124/266). In the per protocol analysis, 57% (51/90) of the dogs had no or mild pruritus at the end of the study. Results for owner-assigned pruritus scores were similar, except that scores were typically 0.4 to 0.5 units higher than those assigned by the investigators.

In the intent-to-treat analysis, mean $\pm$ SD alopecia score decreased from 11.9 ± 5.3 at the time of enrollment to 9.7 ± 3.7 , 8.8 ± 2.7 , 8.8 ± 2.7 , and 8.9 ± 2.8 after 4, 8, 12, and 16 weeks, respectively, of cyclosporine administration. Similarly, in the per protocol analysis, mean alopecia score decreased from 12.05 ± 5.3 at the time of enrollment to 8.2 ± 0.7 at the end of the study. The percentage of dogs with the lowest possible alopecia score (8) increased from 46% (123/266 dogs) at the time of enrollment to 86% (228/266) after 8 weeks and was unchanged thereafter (intent-to-treat analysis). Only 5% (14/266 dogs) of the

dogs had an alopecia score > 12 at the end of the study, whereas 31% (83/266) did at the time of enrollment.

Investigators indicated that treatment response was excellent in 41% of the dogs and good in 28% (intent-to-treat analysis; Table 4). Responses from the owners were similar.

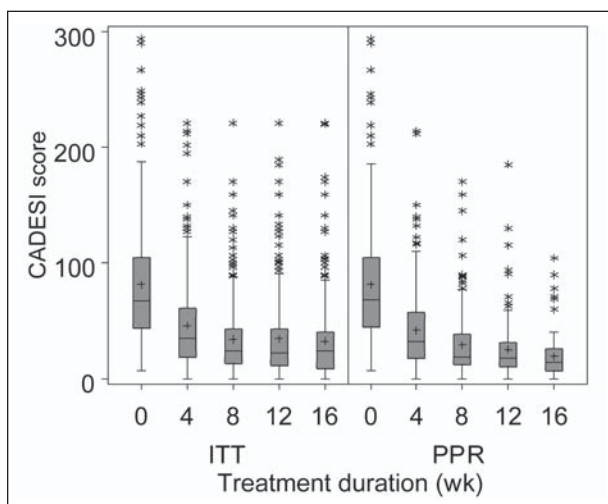


Figure 1—Box plots of canine atopic dermatitis extent and severity index (CADESI; maximum possible score, 360) scores for dogs with atopic dermatitis treated with cyclosporine. Intent-to-treat analyses (ITT) included data for all dogs that were reevaluated. Per protocol analyses (PPR) included data only for those dogs in compliance with the treatment protocol. Each box represents the interquartile range (25th to 75th percentile), with the horizontal line representing the median. Whiskers represent the minimum to the maximum, with the exception of outlying values marked as asterisks, which are values exceeding 1.5 times the upper interquartile range.

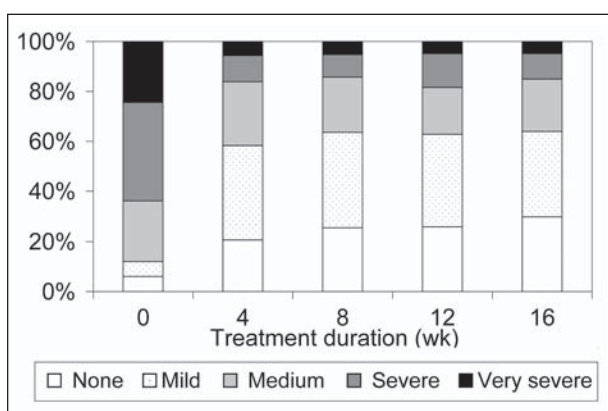


Figure 2—Frequency distribution of pruritus scores over time in dogs with atopic dermatitis treated with cyclosporine.

Four weeks after cyclosporine administration, the dosage was decreased to every-other-day administration in 38% (101/266 dogs; intent-to-treat analysis) and 43% (77/179; per protocol analysis). After 8 weeks, the dosage was further decreased to twice-weekly administration in 11% (28/266 dogs; intent-to-treat analysis) and 14% (17/119; per protocol analysis). At study end, 21% (55/266 dogs; intent-to-treat analysis) and 37% (33/90; per protocol analysis) of the dogs were receiving cyclosporine on a twice-weekly basis.

When dogs were stratified according to body weight, changes in CADESI, owner-assigned pruritus, and alopecia scores, compared with baseline values, were not significantly different among the 3 body weight subgroups. Values were significantly ($P < 0.001$) different from baseline values for all 3 subgroups.

Withdrawal from the study—Eleven (4.1%) dogs were withdrawn from the study because of adverse events. Reasons for withdrawal included vomiting (4 dogs); diarrhea with blood and halitosis, diagnosed as clostridial enteritis (1); vomiting associated with signs of depression and lethargy (1); hepatitis associated with anorexia and lethargy (1); vomiting, diarrhea, and pruritus (1); seizures (1); gingival hyperplasia associated with lethargy, polyuria, and polydipsia (1); and sebaceous cyst (1). Three other dogs did not complete the study because of perceived adverse events, such as pruritus, skin erythema, and otitis externa, that were most likely related to atopic dermatitis.

Adverse events—Vomiting occurred at least once in 82 (31%) dogs while they were receiving cyclosporine. Approximately 60% of these events occurred in the first month of treatment, with the remainder occurring sporadically thereafter. Details on the frequency of vomiting were recorded for 77 dogs. Whereas 73% of these dogs had < 3 vomiting events during the course of the study, 10% had between 4 and 7 events and vomiting was reported as occurring weekly or twice weekly in 6% of the dogs. Multiple episodes of sporadic vomiting were reported for 10% of the dogs. In only 3 dogs was vomiting considered severe. In cases of repeated vomiting, cyclosporine treatment was sometimes interrupted for a few days and then continued without further problems.

Diarrhea or soft feces was reported for 53 (20%) dogs and was associated with vomiting in 10 dogs. In only 1 dog were these signs considered severe. Diarrhea occurred most often during the first few weeks of treatment and resolved without specific treatment in all but 2 dogs. Clostridial enteritis was diagnosed in 1 dog, and

Table 4—Global assessment of the response to treatment, as determined by investigators and owners, in dogs with atopic dermatitis treated with cyclosporine for 16 weeks.

Assessment	Intent-to-treat analysis (n = 266)		Per protocol analysis (215)	
	Investigators	Owners	Investigators	Owners
Poor	31 (12)	31 (12)	18 (8)	19 (9)
Reasonable	40 (15)	37 (14)	33 (15)	29 (13)
Good	74 (28)	77 (29)	61 (28)	65 (30)
Excellent	108 (41)	96 (36)	97 (45)	88 (41)
No response	13 (5)	25 (9)	6 (3)	14 (7)

Values are given as number of dogs (%).
See Tables 1 and 2 for key.

in the other, diarrhea developed after several months of cyclosporine administration and resolved with metronidazole administration. The duration of diarrhea or soft feces was recorded for 40 dogs. A single episode was reported for 17 of the 40 (43%) dogs, whereas diarrhea for 2 to 4 days was reported for 7 (18%) dogs and diarrhea that was episodic, intermittent, or sporadic was reported in 11 (28%) dogs. In 5 (13%) dogs, diarrhea or soft feces lasted > 7 days.

Anorexia or decreased appetite was reported in 8 (3%) dogs and was often associated with episodes of vomiting or diarrhea. Weight loss did not occur except in 1 dog in which unrelated hepatitis was diagnosed.

Gingival hyperplasia was observed in 6 (2.2%) dogs near the end of the study. It was considered severe in only 1 dog.

Seizures were identified in 4 (1.5%) dogs during the study. Seizures were presumed to be related to a brain tumor in 1 dog in which treatment was interrupted, and in another dog, seizures recurred when the dog was no longer receiving cyclosporine. A sibling of the third dog was known to have had seizures. Seizures in the remaining dog remained unexplained. Lethargy was reported in 6 dogs, usually associated with other signs such as anorexia, vomiting, diarrhea, or lameness.

Four dogs had papilloma-like skin lesions. In 2, these lesions resolved spontaneously, and in the other 2, lesions were excised. Cysts were identified in 3 dogs. In 2 of the 3, the cysts were not treated, whereas in the remaining dog, the cyst was removed. Skin nodules were identified in 3 dogs. In 1 dog, these nodules were attributed to insect-bite hypersensitivity. Histologic examination of biopsy specimens from the second dog revealed histiocytic, lymphoplasmacytic, and neutrophilic dermatitis. In the third dog, nodules resolved without treatment. Two dogs developed granulomatous lesions. In one of these dogs, lesions were associated with *Nocardia* infection. Histiocytomas were identified in 3 dogs. The lesion was excised in 1 dog and resolved spontaneously in the other 2.

Lymphadenopathy was identified in 6 dogs but was not considered to be drug related by the investigators. Otitis externa or pinnal erythema with or without exudation occurred in 148 (55%) dogs. Most of these dogs had a history of chronic otitis externa that was presumed to be secondary to atopic dermatitis. During phase 2 of the study, the prevalence of otitis decreased from 53% (142/266 dogs) at the time of enrollment to 37% (90/245) after 4 weeks of cyclosporine treatment and remained stable thereafter. At the end of the study, otitis was reported in 82 of 185 (44%) dogs.

Clinicopathologic testing—For practical reasons, blood samples could not be collected from all dogs at all 3 planned sampling times (enrollment and after 8 and 16 weeks of cyclosporine administration). Results of hematologic testing of all 3 samples were available for 178 dogs, and results of serum biochemical testing of all 3 samples were available for 185 dogs.

Mean values for results of serum biochemical and hematologic testing performed after 8 and 16 weeks of cyclosporine administration were within reference limits.

When values obtained at 8 and 16 weeks were compared with baseline values for individual dogs, small (< 5% of baseline value) but significant increases in some hematology parameters were detected. Hemoglobin concentration, hematocrit, and RBC count were all increased slightly. White blood cell count decreased, whereas lymphocyte count (absolute count and relative fraction) increased.

Few significant changes from baseline values were identified for biochemical variables, and changes that were identified were generally small. Creatinine concentration was significantly ($P < 0.005$) increased by 6% and 4%, compared with baseline values, after 8 and 16 weeks, respectively. Urea nitrogen and serum protein concentrations were significantly ($P < 0.001$) increased by 5% and 4%, respectively, after 16 weeks. Serum urea nitrogen concentration was greater than the upper reference limit (16 mg/dL) after 8 or 16 weeks in 15 of 266 (5.6%) dogs and was greater than the upper reference limit in 8 (3%) dogs at both times. A significant increase in the serum urea nitrogen-to-creatinine ratio was not found. There was a significant increase (15%) in cholesterol concentration, compared with baseline concentration, during treatment, and hypercholesterolemia was identified in 7 (2.6%) dogs. Alanine aminotransferase and alkaline phosphatase activities significantly decreased by 5% to 10%. No significant changes in glucose or bilirubin concentration were identified. Electrolyte concentrations remained unchanged except for calcium concentration, which was significantly ($P = 0.01$) lower at study end (9.86 mg/dL) than at the time of enrollment (10.03 mg/dL). Calcium concentration remained within reference limits in all except 2.3% of the dogs in which concentration was low.

Urine samples could not be obtained from all dogs at all 3 sampling times. Thus, complete data with all laboratory analyses were available for only 94 dogs. No significant changes relative to baseline values were observed for urine pH or specific gravity. Proteinuria was identified at the time of study enrollment in 47 of 105 (45%) dogs. There was no trend for increased frequency of proteinuria over the study. Glucosuria was not detected at any time. Urine WBC count and bilirubin concentration were significantly ($P < 0.05$) increased after 8 or 16 weeks of cyclosporine administration.

Bacteriuria was identified at the time of enrollment in 21 of 89 (24%) dogs, and 9 of these dogs still had bacteriuria at the end of the study. Of the 68 dogs without bacteriuria at the time of study enrollment, 44 remained negative for bacteriuria after 8 and 16 weeks, 10 were positive for bacteriuria at 8 and 16 weeks, and 14 were positive for bacteriuria at 8 or 16 weeks. No clinical signs of urinary tract infection were observed, except in 1 dog with cystitis.

Discussion

Results of the present study suggest that administration of cyclosporine at a dosage of 5 mg/kg, PO, every 24 hours is efficacious for the treatment of atopic dermatitis in dogs. Furthermore, our results confirm that the frequency of cyclosporine administration can be reduced following an initial induction period.

Only dogs with nonseasonal dermatitis were included in the present study, as it has been shown pre-

vously that signs may resolve spontaneously in dogs with seasonal dermatitis.² In the present study, no improvement was evident after 4 weeks in the dogs that received the placebo, suggesting that previous treatments such as immunotherapy or concomitant treatments such as antimicrobials and antifungals did not contribute to the clinical improvement seen in the dogs given cyclosporine. The significant improvements in CADESI and pruritus scores were similar to those reported previously.²

Results of the present study were similar to results of a European study⁴ in which the same dosage and clinical parameters were used, even though breeds included and climatic conditions were different between studies. Thus, the response to cyclosporine appears consistent across disparate populations.

In the European study,⁴ cyclosporine dosage was decreased on the basis of improvements in the CADESI score, whereas in the present study, the dosage was decreased on the basis of improvements in both the CADESI and the owner-assigned pruritus score. However, this difference did not appear to alter the dosing regimen, as the percentage of dogs in the present study (41%) in which dosing frequency was reduced to every other day after 4 weeks was similar to the percentage in the previous study (50%).⁴ After 12 weeks of treatment, 28% of the dogs were receiving cyclosporine twice a week in the present study, compared with 26% in the previous study. These observations suggest that the dosage can be decreased on the basis of either CADESI or pruritus score.

Frequency with which concomitant treatments such as antimicrobials and antifungals were used in the present study was not analyzed. The similarity between responses in the present study and the previous European study,⁴ however, suggests that these treatments did not substantially affect the response to cyclosporine.

Extent of hair loss was used as a measure of clinical efficacy in the present study. Cyclosporine has been shown to stimulate hair growth, probably through its effects on hair follicles in the anagen phase.⁸ In the absence of a control group, the relative effects of the resolution of inflammation and the reduction in pruritus versus direct effects of cyclosporine on hair regrowth are difficult to assess. To our knowledge, hair regrowth has never been measured in clinical studies involving other treatments; therefore, it is difficult to evaluate whether hair regrowth was related to cyclosporine administration. Although hair growth was consistently observed, hypertrichosis (excessive hair growth) was not seen in any of the treated dogs in the present study.

The initial dosage of cyclosporine ranged from 3.3 to 6.6 mg/kg, PO, every 24 hours in the present study, as single capsules or a combination of 2 capsules containing 10, 25, 50, or 100 mg of cyclosporine were used to obtain the dose for each dog. We found that in this dosage range, there was no relationship between dosage and clinical response after 4 weeks. This suggests that clinical response plateaus at dosages higher than 3.3 mg/kg. However, in a previous study,² a dosage of 2.5 mg/kg, PO, every 24 hours was found to be significantly less effective than a dosage of 5 mg/kg, PO, every 24 hours.

The second phase of the present study was designed to test the efficacy of cyclosporine as the dosage was decreased and the safety of the drug in a large population of dogs. Statistical analyses were conducted on data for dogs that fulfilled the protocol requirements (per protocol analyses) but also on data for the entire population of dogs for which at least 1 follow-up evaluation was made (intention-to-treat analyses). Given the duration of the study, it was not unusual that a relatively large number of dogs were excluded because of deviations from the protocol. It was therefore important to conduct both per protocol and intention-to-treat analyses to assess the impact of exclusions or withdrawals on the overall clinical response.

The efficacy determined after per protocol analyses was indeed better than that obtained after intention-to-treat analyses, but the difference was small and not clinically relevant. This can be explained by the fact that most dogs were not excluded because of poor efficacy but because of deviations from protocol, such as reevaluations outside the requested time period or the occasional administration of medicated shampoos. It should also be noted that exclusions from the study occurred most often after 8 weeks when most of the clinical improvement had already been obtained. Use of the last-observed-value-carried-forward protocol meant that missing values were replaced by values close to the values we would have expected to obtain at the end of the study.

Cyclosporine was found to be generally safe in the present study, with only a few dogs (4.1%) not completing the study because of adverse events that may or may not have been related to cyclosporine administration. As reported in earlier studies,^{2,4} vomiting and gastrointestinal tract signs were the most common adverse events and generally were mild, requiring medical intervention only in rare instances. Gastrointestinal tract signs appeared most often in the first few weeks of treatment, and the number of episodes usually was small, compared with the number of treatment days.

Because impaired renal function is the most frequent adverse event associated with cyclosporine treatment in humans, particular attention was given to biochemical variables indicative of a change in renal function in the present study. A significant but small increase (< 10%) in serum creatinine and urea nitrogen concentrations was found, but the urea nitrogen-to-creatinine concentration ratio remained unchanged. Creatinine concentration was higher than the upper reference limit after 8 and 16 weeks of cyclosporine administration in only 2.8% of the dogs. In addition, the number of dogs with proteinuria remained stable, as did serum electrolyte concentrations. Thus, there was little evidence of impaired renal function in dogs in the present study. Similarly, in a toxicity study⁹ in which cyclosporine was administered at dosages as high as 45 mg/kg/d (20.5 mg/lb/d) for a year, no remarkable macroscopic or microscopic renal lesions were found. In other clinical studies^{2,4} of the microemulsion formulation of cyclosporine, increases in serum creatinine concentration were not observed.

Because of cyclosporine's immunomodulating effects, the frequency of urinary tract infections was

evaluated by monitoring dogs for bacteriuria. A surprisingly high percentage of dogs (23%) had bacteriuria at the time of enrollment, possibly because of previous glucocorticoid administration for treatment of chronic atopic dermatitis. A recent study^f confirmed the high prevalence of urinary tract infections in dogs receiving glucocorticoids for prolonged periods. In the present study, the prevalence of bacteriuria was essentially unchanged during cyclosporine treatment, with temporary fluctuations or conversion from negative to positive and vice versa. The lack of increase in prevalence of bacteriuria during the study argues against the hypothesis that cyclosporine administration could promote urinary tract infections. This finding is supported by the results of an unpublished 90-day study performed by the manufacturer in which bacteriuria was not documented in any samples from treated dogs, even when they were given cyclosporine at a dosage of 30 mg/kg/d (13.6 mg/lb/d) for 3 months.

The frequency of otitis externa was high among dogs enrolled in the present study, probably as a consequence of atopic dermatitis,¹⁰ but decreased markedly during the first 4 weeks of treatment. This suggests that cyclosporine did not adversely affect immune defenses against ear infections. A similar beneficial effect of cyclosporine for treatment of end-stage otitis externa has been reported previously.⁸

Verrucous (papilloma-like) skin lesions were observed in 4 dogs in the present study (1.5% of treated dogs). Analogous lesions have been reported in dogs receiving cyclosporine at similar dosages^{3,11} as well as in laboratory studies^{9,12} in which cyclosporine was administered at high dosages. The etiology of such lesions remains the subject of controversy. Histologic, ultrastructural, immunohistochemical, and DNA amplification techniques have failed to consistently demonstrate classical papillomavirus in these lesions.^{9,12,h} Failure to respond to antimicrobial administration suggests that they are not the result of a bacterial skin infection. In the present study, lesions spontaneously resolved in 2 dogs, and spontaneous resolution of these lesions following cessation of drug administration has been reported previously.^{9,12} It is hypothesized that these verrucous skin lesions could result from an overgrowth of cutaneous tissues caused by cyclosporine-mediated inhibition of collagen degradation secondary to stimulation of fibroblast proliferation¹³ and low collagenase expression.¹⁴ Gingival hyperplasia, also rarely observed in the present study (6 dogs), could result from the same cyclosporine-induced effects on connective tissues and epithelial cells.

In conclusion, results of the present study confirm that a marked improvement in skin lesions and pruritus is obtained in the first 4 weeks after initiating cyclosporine treatment in dogs with atopic dermatitis and that beneficial effects can be maintained with a tapering dosage regimen. Treatment effect could not be predicted from the initial severity of skin lesions or pruritus, but the response to cyclosporine appeared to be consistent and not influenced by breed or environmental conditions. The drug was well tolerated, with the most frequent adverse reactions being transient gastrointestinal tract signs.

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