

Evaluation of the clinical efficacy of cyclosporine in atopic dogs treatment

Avaliação da eficácia da ciclosporina no tratamento de cães atópicos

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Abstract

Atopic dermatitis (AD) is an inflammatory, pruritic and chronic allergic skin disease. It is recognized as the second-most common allergic skin disease of dogs, after flea allergy. Pruritus is the predominant sign of canine AD, and it affects a variety of areas of the body, leading to intense suffering in both the animal and its owner. The long-term use of glucocorticoid therapy can be devastating because of its numerous side effects and secondary diseases. Cyclosporine (CsA) has been considered a good therapeutic option to treat canine AD. CsA inhibits the activation of cells that initiate the cutaneous immune response (Langerhans cells and lymphocytes) and that mediate allergic reactions (mast cells and eosinophils). It also decreases the release of histamine and other cytokines. The objective of this study was to analyze the efficacy of CsA (5 mg/kg, SID for 60 days) to reduce skin lesions and pruritus in 21 atopic dogs using CADESI-03 and two scales to quantify the levels of body itching. This immunomodulatory therapy was considered to be an effective treatment for atopic dogs because it reduced skin lesions by 70% after 60 days of therapy. During that period, there was a 52.6% reduction of body itching as assessed via a verbal numeric scale, and there was a significant reduction of body itching on a qualitative scale, as the maximal levels of pruritus ("three" and "four") were hardly observed after immunomodulatory therapy. CsA was effective and safe in the treatment of canine atopic dermatitis.

Keywords: Atopic dermatitis. Pruritus. Cyclosporine. Dogs.

Resumo

A atopia ou dermatite atópica é uma doença inflamatória pruriginosa, crônica e recorrente reconhecida como a segunda alergopatia mais comum, estando aquém apenas da dermatite alérgica à picada de pulgas. Esta doença é caracterizada pela presença exacerbada de prurido corpóreo, infringindo sofrimento ao paciente e desalentando seu proprietário. Por se tratar de uma doença de longo decurso, o tratamento com glicocorticoides pode causar diversos efeitos adversos, além de doenças mais graves. Como alternativa ao tratamento de cães atópicos, a ciclosporina (CsA) acaba tornando-se uma boa opção terapêutica. A CsA inibe as funções das células que iniciam a resposta imunológica (células de Langerhans e linfócitos) e das células que efetuam a resposta alérgica (mastócitos e eosinófilos) e, também, diminui a liberação de histamina e de várias citocinas. O objetivo do presente estudo incluiu a: análise da eficácia da CsA (5mg/kg, SID durante 60 dias) na redução de lesões corpóreas e do prurido com auxílio do CADESI-03 e de duas escalas de prurido corpóreo. A CsA mostrou-se eficaz no tratamento da dermatite atópica canina pois reduziu as lesões corpóreas em 70% após 60 dias de terapia. Nesse mesmo período ocorreu redução da intensidade do prurido corpóreo em 52,6%, avaliado através da escala numérica verbal; e observou-se redução significativa na escala qualitativa de prurido corpóreo, uma vez que os níveis máximos de prurido ("três" e "quatro") quase não foram observados após a terapia imunomodulatória. A CsA mostrou-se eficaz no tratamento da dermatite atópica canina.

Palavras-chave: Dermatite atópica. Prurido. Ciclosporina. Cães.

Introduction

Atopic dermatitis (AD) is a common dermatosis that affects dogs and is defined as an inflammatory pruritic dermatopathy. It is chronic and recurrent and genetically determined, with characteristic clinical manifestations usually associated with the production of IgE antibodies, which are specific for environmental allergens¹.

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Currently, a new class of AD is being proposed that should be differentiated from AD: “atopic dermatitis-like” (AD-like) disease. AD-like disease presents the same clinical manifestations as AD, but the presence of IgE antibodies specific against environmental allergens has not been fully confirmed^{2,3,4}.

AD affects between 3 to 15% of the canine population^{5,6,7}.

Due to chronic and relapsing characteristics of AD and the fact that it drastically reduces the quality of life of its carriers, there is a constant need to study different therapeutic approaches with the goal of replacing chronic corticosteroid use due to their devastating side effects.

Cyclosporine (CsA) is a liposoluble cyclic polypeptide metabolite derived from the fungus *Tolypocladium inflatum gams*. This drug forms a complex with an intracellular protein, cyclophilin-1, and this complex in turn inhibits calcineurin, an enzyme that synthesizes IL-2. The absence of this interleukin hinders the activation and proliferation of T lymphocytes as compared to other cytokines, such as IL-4 and INF- γ . Other characterized effects of CsA include its ability to decrease the survival and degranulation of mast cells; inhibit the release of IL-4, IL-5, TNF, IL-3 and IL-8; inhibit eosinophil survival and recruitment to the site of inflammation; decrease the number and antigen-presenting function of Langerhans cells; decrease the release of keratinocyte cytokines; decrease mast cell-dependent cellular infiltration; and decrease IgE in cutaneous inflammation sites by preventing the TNF-mediated late-phase reactions^{8,9}.

In veterinary medicine, CsA is indicated for the control of immunomediated and autoimmune diseases, such as perianal fistulas, complex pemphigus, pemphigoid-bullous, sebaceous adenitis, atopic dermatitis, sterile nodular panniculitis, alopecia areata and Sézary syndrome, among others^{10,11}. The efficacy and safety of CsA for the control of AD has been

documented by several foreign and Brazilian authors^{12,13,14,15,16,17,18}.

The present study aimed to evaluate the efficacy of oral administration of CsA (5 mg/kg, SID for 60 days) in the treatment of AD through the evaluation of the score of corporal lesions and two different scales of pruritus using the case series of the Dermatology Division (DD) of the Department of Clinical Medicine (DCM) and the Veterinary Hospital (VETHO) of the School of Veterinary Medicine and Zootechnology of the University of São Paulo (Faculdade de Medicina-Veterinária e Zootecnia da Universidade de São Paulo – FMVZ/USP).

Material and Method

The experimental group included 21 dogs with AD diagnosed by the DD of the DCM VETHO of the FMVZ/USP without any restriction regarding breed, gender or age.

Dogs with a pre-established diagnosis of AD with moderate (“grade” 5 or 6) or intense (“grade” 7-10) manifestations of body pruritus (seasonal or perennial), as determined by the verbal numerical rating scale, and with level three or four pruritus, as determined by the body pruritus qualitative scale as proposed by Hill¹⁹ and its subsequent modifications (Appendix A), were selected. The following animals were included in the study or removed during the course of the study: carriers of epilepsy, nephropathy or hematopathy; those from owners or representatives not aware of the clinical condition, temper, mode of conduct or correct handling, hygiene and sanitation of the patients; those with known previous conditions of altered blood pressure, hematic background or serum biochemistry; those not properly submitted to the experimental protocol or clinical follow-up; and those seropositive for leishmaniasis. For inclusion in the experimental study, a diagnosis of AD was made based on the symptomatic and lesion features and by

excluding other primary mimetic pruritic dermatopathies (scabies, tropho-allergic dermatitis or siphonaptera bites) via additional examination.

The devised protocol involved the application of cyclosporine (SandimmunNeoral® – Novartis, oral solution, 100 mg/mL) at a dosage of 5 mg/kg weight, *per os*, every 24 hours for 60 days. Assessments were performed 15, 30 and 60 days after the first appointment (Day 0).

Bathing was recommended every 5 days using warm water and emollient soap (Dove®) followed by rinsing with plenty of water and drying without the aid of a hot blow dryer. Animals presenting secondary pyoderma underwent systemic antibiotic therapy (amoxicillin with potassium clavulanate, *per os*) at the standard dosage of the DD (DCM-VETHO/USP). This drug was selected due to the lower risk of emetic episodes so as not to interfere with the effects of CsA therapy.

During the course of the study, all animals were submitted to a strict control of ticks and fleas using the ectoparasiticide (Advantage max 3®) commonly employed in the therapy scheme and the standard prophylactic of the DD.

The protocol was suspended and orthodox steroid therapy was adopted whenever side effects appeared (tegumentary or systemic), the protocol proved ineffective or as specifically requested by the owner.

The animals under anti-pruritic steroid therapy at the time the study were gradually (≤ 21 days) withdrawn simultaneously with the introduction of the new protocol. Isolated cyclosporine therapy was also performed over the same period at the end of the study.

On the first appointment and on the three subsequent scheduled visits, the following analyses were performed:

a) Classification and quantification of skin lesions using the Canine Atopic Dermatitis Extent and Severity Index (CADESI-03) score²⁰, which is a scale of severity from 0 to 5. A total of 62 different body regions were analyzed. CADESI-03 was used on the first

appointment and on the scheduled rechecks 30 and 60 days later. If on the last visit (Day 60) the subject presented a 50% or greater decrease in the CADESI-03 score, a recommendation was made to administer cyclosporine every 48 hours.

b) Determination of the presence and/or the intensity of pruritic symptoms at the time of enrollment and during clinical follow-up. Pruritus was assessed by interviewing the owners or representatives using the verbal numerical scale and qualitative levels modified from those originally proposed by Hill¹⁹. This evaluation was performed at Days 0 (first appointment), 15, 30 and 60. Qualitative levels of body pruritus were included in the circular graphical representation (Figure 1) so that owners would not confine themselves to use just the numerical pruritus scale but would also be aware to behavioral changes.

For the qualitative variables, absolute (n) and relative (%) frequencies were presented; for the quantitative variables, the mean and median were calculated as a summary metric. The minimum, maximum and standard deviation values were used as measures of variability.

The data for quantitative variables were compared at the different stages (D- 0, D- 15, D- 30, D- 60), and a repeated measures analysis of variance was used as the statistical test. The results are shown below each table of the following section at a significance level of 5%; i.e., the significance is indicated by a p-value < 0.05 (highlighted in blue). To use this test, the group variance homogeneity was evaluated, which is a necessary assumption. If a difference between stages was detected, multiple comparisons were performed to identify which groups differed (paired comparisons at the different stages) by the Bonferroni test. A significance level of 5% was also used for this test.

Results

Thirty-nine dogs, without any restriction of breed, gender or age and with a set diagnosis of AD, were

enrolled in the study. From these, 18 were excluded for meeting at least one of the previously described exclusion criteria. The remaining 21 animals followed the protocol to completion.

The summary metrics (value and median) and measures of variance (minimum, maximum and standard deviation) of the quantitative variables (age and weight) did not change throughout the trial. However, some statistically significant differences ($p < 0.05$) in CADESI-03 score values were observed at different time points (Days 0, 30 and 60), and the highest value was obtained at the start of the study (Table 1).

As assessed by the verbal numerical scale, changes were observed in body pruritus at the different times of evaluation (Table 2). Multiple comparisons revealed statistically significant changes ($p < 0.001$) between the starting stage and the remaining stages, with larger values in the pruritus scale than the rest. There was also a difference in the pruritus values between Days 15 and 60. However, no significant differences were observed between the follow-ups at Days 15 and 30 or between Days 30 and 60.

Regarding body pruritus as assessed by the qualitative pruritus scale, there were also differences between the defined stages (Table 3). A significance level of 5% was used; i.e., a difference was considered significant at a p -value < 0.05 . At the first stage, there was a higher percentage of high values of the scale as compared with the other stages. At Day 0, there were no values of 0 or 1 on this scale.

After 60 days of treatment with CsA, 11 out of the 21 dogs (52.4%) presented a decrease in the CADESI-03 score of at least 50%. For this subset of specimens, CsA was subsequently administered once every 48 hours. Six dogs (28.6%) did not show the expected signs of improvement and continued to receive CsA on a daily basis. Treatment was interrupted for four specimens (19%) during the last check-up step either due to an evident improvement of their clinical pic-

ture and/or at the owner's request, as the high cost of the drug would have to be supported exclusively by the owner.

Discussion

Tegumentary lesions as quantified by CADESI-03 were significantly reduced when comparing the starting stage (D- 0) to the other stages (D- 30 and D- 60). After 30 days of CsA treatment, a 52.3% decrease in the CADESI-03 index was observed. After 60 days, this decrease reached 70%. These data proves the efficacy of CsA in reducing the number of skin lesions (primary or crusted) stemming from AD, which is in agreement with previous studies^{12,13,14,15,17}. In the present study, a larger percentage of lesion involution occurred in the first 30 days, as was observed in the study by Steffan, Parks and Seewald¹⁷.

Pruritus assessment via the verbal numerical scale revealed a statistically significant difference between the starting stage (D- 0) and the remaining stages (D- 30 and D- 60) and also between Day 15 and Day 60.

After 15 days of CsA treatment, a gradual decrease of up to 36% in pruritus intensity was observed. This percentage increased to 45% and 52.6% after 30 and 60 days, respectively, proving the efficacy of CsA in the relief of this symptom.

The results obtained using the body pruritus qualitative scale revealed a statistically significant difference between the different stages. On Day 0, pruritus level "three" was the most common (57.1%), followed by levels "four" (23.8%) and "two" (19%). On Day 60, level "one," which had not been observed on Day 0, became the most prevalent (47.6%), followed by levels "zero" (28.6%), "two" and "four" (9.5% each) and "three" (4.8%). Therefore, after 60 days of CsA therapy, the incidence of the maximum level of pruritus, level "four," had decreased from 23.8% to 9.5%, whereas the incidence of level "three" decreased from

Table 1 – Mean CADESI-03 scores for body lesions in dogs with atopic dermatitis undergoing cyclosporine therapy. DD, VETHO-FMVZ/USP - São Paulo - 2010

	Mean	Median	Standard Deviation	Minimum	Maximum
Day 0	48.3	26.0	58.6	8.0	272.0
Day 30*	25.3	15.0	25.6	0.0	106.0
Day 60*	14.5	15.0	14.2	0.0	42.0

p-value = 0.040

*statistically significant difference ($p < 0.05$) relative to the starting point.

Table 2 – Mean values of pruritus intensity as assessed via the verbal numerical scale of dogs with atopic dermatitis undergoing cyclosporine therapy. DD, VETHO – FMVZ/USP - São Paulo -2010

	Mean	Median	Standard Deviation	Minimum	Maximum
Day 0	7.8	8.0	1.0	5.0	9.0
Day 15*	5.0	5.0	2.0	1.0	8.0
Day 30*	4.3	4.0	2.2	1.0	8.0
Day 60*#	3.7	3.0	2.3	0.0	8.0

p-value <0.001

*statistically significant difference ($p < 0.05$) relative to the Day 0 value.

#statistically significant difference ($p < 0.05$) relative to the Day 15 value.

Table 3 – Mean values of pruritus intensity (n and %) as assessed by the qualitative scale of atopic dermatitis in dogs undergoing cyclosporine therapy. DD of VETHO – FMVZ/USP - São Paulo - 2010

Scale	Day 0		15 days*		30 days*		60 days*	
	n	%	n	%	n	%	n	%
0	-	-	2	9.5	6	28.6	6	28.6
1	-	-	13	61.9	9	42.9	10	47.6
2	4	19.0	3	14.3	4	19.0	2	9.5
3	12	57.1	2	9.5	-	-	1	4.8
4	5	23.8	1	4.8	2	9.5	2	9.5

p-value < 0.001

*statistically significant difference ($p < 0.05$) relative to Day 0.

57.1% to 4.8%. These results clearly indicate a significant improvement of body pruritus as assessed by another less subjective scale.

Fontaine and Olivry¹² reported a 100% decrease in the magnitude of pruritus after 14 days of treatment.

The authors reported a larger decrease in the pruritus score as compared to the lesion score, which decreased by 60%. This might be due to the shorter time span of that study, which was insufficient to allow evident remission of chronic lesions.

Lucas et al.¹⁸ reported that out of 22 atopic canines, 15 (68.2%) had a satisfactory reaction to CsA treatment, of which 13 (59%) were fully healed from pruritus and 2 (9.2%) improved by 75%.

The results in this study showed that lesion remission is more significant than pruritus remission (70% vs. 52.6%) after eight weeks of therapy according to the verbal numerical scale. These results contradict those of Fontaine and Olivry¹², who concluded that pruritus remission was significantly greater than lesion remission after 14 days. However, they also claimed that the short time span of their study would be insufficient to allow evident involution of chronic lesions.

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Conclusion

Regarding the methodology employed in this study, it is possible to conclude that *per os* CsA therapy at a single daily dosage of 5 mg/kg for 60 consecutive days constitutes an effective pharmaceutical option because of the following:

- it initiated and maintained a decrease in body pruritus as measured by qualitative and quantitative scores (verbal and qualitative numerical scales) after 15, 30, and 60 days of therapy, and
- it resulted in a decrease of elementary skin lesions according to a score of extent and severity (CADESI-03), after 30 and 60 days of treatment.

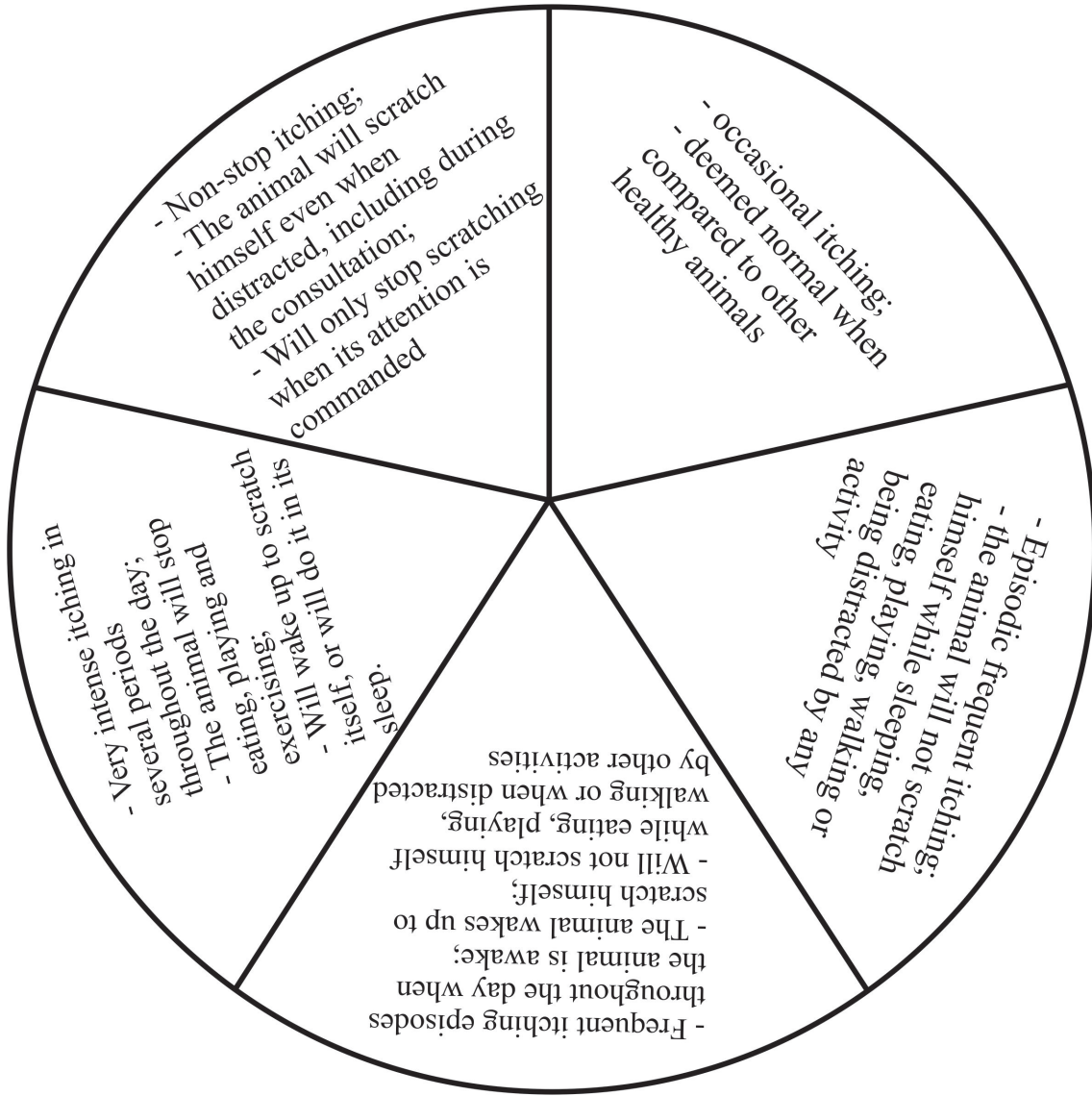


Figure 1 - Qualitative levels of body pruritus. Modified (Hill)¹⁹