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A randomized double-blinded placebo-controlled study to evaluate an effective ciclosporin dose for the treatment of feline hypersensitivity dermatitis

Stephen King*, Claude Favrot†, Linda Messinger‡, Tim Nuttall§, Jean Steffan*, Sophie Forster* and Wolfgang Seewald*

*Novartis Animal Health, Schwarzwaldallee 214, Basel, Switzerland
†Dermatology Department, Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland
‡Veterinary Referral Center of Colorado – Dermatology/Allergy, 3550 South Jason Street, Englewood, CO 80110, USA
§Department of Infection Biology, School of Veterinary Science, The University of Liverpool, Leahurst Campus, Neston, UK

Correspondence: Stephen King, Novartis Animal Health, Schwarzwaldallee 214, Basel, Switzerland. E-mail: stephen.king@novartis.com

Background – Hypersensitivity dermatitides (HD) are frequently suspected in cats, but there are few clinical studies on safe and effective treatments in the published literature.

Objectives – To establish a safe and effective dose of ciclosporin in the treatment of feline HD.

Animals – One hundred client-owned cats with feline HD.

Methods – Double-blind study, with cats randomly assigned to receive ciclosporin at either 7.0 mg/kg once daily (n = 33) or 2.5 mg/kg once daily (n = 32) or a placebo (n = 35) for 6 weeks.

Results – Mean Total Lesion Scores with 7.0 mg/kg ciclosporin were significantly lower than with 2.5 mg/kg ciclosporin (P = 0.0047) or placebo (P = 0.0003) at study end. Individual Total Lesion Scores improved by >50% in 70% of the 7.0 mg/kg group, compared with 47% in the 2.5 mg/kg group and 23% in the placebo group (P = 0.0006). The investigators' Global Assessment of Improvement was 'excellent' or 'good' in 61% of cats treated with 7.0 mg/kg ciclosporin, compared with 47% of cats given 2.5 mg/kg and 23% given placebo. The improvement in Investigator Pruritus Scores was significantly greater in cats treated with 7.0 mg/kg ciclosporin (54%) compared with both 2.5 mg/kg ciclosporin (32%; P = 0.0232) and placebo (21%; P = 0.0063). Mild gastrointestinal disorders were the most common adverse events, but these did not require cessation of therapy.

Conclusions and clinical importance – Results suggest that 7.0 mg/kg ciclosporin once daily in food or *per os* for 6 weeks is effective and well tolerated in feline HD.

Introduction

Hypersensitivity dermatitides (HD) are frequently suspected in cats, but there are few published clinical studies and most of the data have been drawn from the observations of individual dermatologists.[1–4] Hypersensitivity dermatitis is a general term that usually encompasses flea-bite hypersensitivity, urticaria, angioedema, food-induced hypersensitivity dermatitis, contact dermatitis and atopic dermatitis.[4] It is usually accepted that allergic cats exhibit pruritus and at least one of the following pattern of lesions: head and neck excoriations or ulcerations; self-induced alopecia; eosinophilic granuloma complex (eosinophilic plaque, eosinophilic granuloma, indolent ulcers and fat chin); and miliary dermatitis. It is, however, worth noting that none of these signs or patterns is pathognomonic of an allergic disease.[2,5]

Treatment of HD in cats generally relies on glucocorticoids, antihistamines, allergen-specific immunotherapy, fatty acids, special diets selected following food elimination diet trials, flea control/avoidance and, more infrequently, megestrol acetate.[1] Treatment with corticosteroids and megestrol acetate is not always satisfactory because adverse effects are not uncommon. The efficacy of antihistamines has not been clearly demonstrated, having been assessed only in an open single-arm study.[6] Hyposensitization has been evaluated in several open studies, and success has been reported in 50–75% of cases.[7,8] Despite this, hyposensitization may not commonly be used, because identification of the offending allergens can be difficult. The use of ciclosporin in the treatment of feline HD with clinical signs of pruritus, excoriation/ulceration, self-induced alopecia and eosinophilic granuloma complex has been reported in small uncontrolled pilot studies[9] and retrospective studies.[10] In these studies, feline HD-associated pruritus and lesions responded well (improvement in the range of 50–75% after 30–60 days) to ciclosporin with greater than half of

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the treated cats demonstrating a response to therapy. In a further randomized double-blinded study[11] comparing ciclosporin with prednisolone in the treatment of feline HD, there was no significant difference in the degree of remission or in the number of cats that responded. Ciclosporin appeared to be well tolerated in these studies, and the most frequently reported adverse reactions were gastrointestinal disorders.

Most of these studies, however, involved limited numbers, with no more than 20 cats treated with ciclosporin in any single trial. In addition, none of the studies was placebo controlled and most were not blinded (except for the ciclosporin–prednisolone comparison).[11] The assessment of the response, moreover, was not standardized nor quantified consistently. Different efficacy criteria were used, including a composite lesion score similar to the canine atopic dermatitis extent and severity index (CADESI),[9,11] frequency of remission, [10] and a qualitative assessment of the improvement of the clinical signs[10] at various time points. Furthermore, these studies used a range of doses of ciclosporin from 3.6 to 13.3 mg/kg daily,[9,10] meaning that the effective dose has not been sufficiently established. The objective of the present study was to confirm an effective dose of ciclosporin given as a microemulsion formulation (modified ciclosporin) in the treatment of feline HD.

Material and methods

Study design

This was a 6 week, prospective, multicentre, randomized, double-blind, placebo-controlled pivotal field study to compare the efficacy and safety of ciclosporin at either 2.5 mg/kg once daily (low dose) or 7.0 mg/kg once daily (high dose) with a placebo control in the treatment of feline HD. Cats remained with their owners in their usual home for the duration of the study. Owners had to provide informed consent prior to enrolment and were free to withdraw at any point. The study was conducted in accordance with the Procedures and Principles of Good Clinical Practice.

Enrolment criteria

Recruited cats were client owned, at least 6 months of age, and weighed a minimum of 2 kg. They must have had a history of year-round pruritus and at least one of the following lesions: miliary dermatitis (MD); facial or neck excoriation (E); self-induced alopecia (SA); and/or eosinophilic plaque (EP). The cats were recruited from 24 veterinary clinics across Europe and the USA. Investigators were selected based on their experience in small animal dermatology and most were board-certified veterinary dermatologists.

Flea-bite hypersensitivity was ruled out by use of flea adulticides and environmental treatment for at least 2 months in the majority of cases, or 1 month based on the clinical judgement of the individual investigator (in some areas that were not considered to be flea endemic, a flea adulticide was not administered). Primary bacterial and fungal infections were eliminated via appropriate cytology, culture and treatment prior to enrolment. Six week food trials with novel ingredients or hydrolysed proteins were used to eliminate food allergies, although these could not be completed in all cats (15 of 100 cats). In addition, cats had to be feline leukaemia virus and feline immunodeficiency virus negative and to have their *Toxoplasma* serology status assessed prior to inclusion. In the USA, cats with *Toxoplasma*-positive serology titres were excluded. In the EU, no exclusion was made based on *Toxoplasma* serology titres. In individuals that had not previously been sampled, skin biopsies were collected as an aid in the diagnosis of neoplastic and immune-mediated conditions. Other exclusion criteria were as follows: pregnancy, lactation or intention to breed during the study; requirement for vaccination during the study; active systemic infection; evidence or history of any type of malignancy; uncooked home-prepared diet (due to variability in constituents and the potential for transmission of *Toxoplasma*); and lesions localized only to the mouth, oral cavity and upper lip. The owners were also instructed not to change the home management or diet of their cat during the study unless requested by the investigator for reasons unrelated to the allergic condition.

Use of the following treatments was prohibited during the study, with wash-out periods as indicated in parentheses prior to enrolment: systemic glucocorticoids, megoestrol acetate (28 days); topical and ophthalmic glucocorticoids, antihistamines, serotonin reuptake inhibitors, topical calcineurin inhibitors, vaccinations (14 days); ketoconazole, itraconazole, erythromycin or phenobarbital (7 days); essential fatty acids (56 days, unless maintained on the same regime throughout); and shampoos (14 days, unless maintained on the same regime throughout). If the response to allergen-specific immunotherapy was considered unsuccessful by the investigator and the cat qualified for inclusion, a withdrawal period of 14 days was required after the last injection.

The use of topical and/or systemic antibiotics was permitted. In cases of severe facial/neck pruritus, at the investigator's discretion, an Elizabethan collar could be used at study initiation up to a maximum of 10 days thereafter. Cats received a monthly flea adulticide treatment for the duration of the study except in US regions not considered flea endemic.

Experimental protocol

Ciclosporin was provided by Novartis Animal Health (Basel, Switzerland) as a 100 mg/mL micro-emulsion liquid formulation contained in a glass bottle, administered orally, once daily for 6 weeks. The placebo formulation was similar in appearance to the active formulation and was presented in identical bottles with matching labelling. The treatments were administered using either a mini-pump or a syringe. The mini-pump device was placed on the bottle containing the test formulation and activated manually to deliver a standardized volume of solution. Both delivery options were precisely calibrated to deliver the required volume with less than a 5% variation in accuracy. Ciclosporin was mixed with a small quantity of food, and the owners were instructed to withdraw the cat's food for a sufficient period prior to dosing to encourage the cat to eat the medicated food. If the cat completely or partly refused the medicated food for two consecutive days, the owner was instructed to administer the treatment directly into the cat's mouth using the mini-pump or the syringe immediately after feeding.

Cats were randomly allocated using block randomization to receive 7.0 mg/kg ciclosporin (high dose), 2.5 mg/kg ciclosporin (low dose) or placebo, with the same number of cases in the three treatment groups (each block contained two low-dose, two high-dose and two placebo treatments). The placebo group was subdivided into a high- and low-volume group to match the treatment volumes in the two ciclosporin groups and preserve blinding to treatment allocation. A unique randomization list centrally generated by a statistician was provided for each investigator site. No separate randomization schedule was prepared for sex, age or body weight.

Assessment of efficacy

The study consisted of four visits (prestudy to determine inclusion suitability and days 0, 21 and 42). Cats were assessed and assigned treatment on day 0, with treatment initiated on day 1. All efficacy parameters were recorded on day 0 (baseline), then at day 21 (±3 days) and day 42 (±3 days) by the same investigator.

Each lesion type (E, MD, EP and SA) was scored independently. A numerical rating scale with five degrees of severity [0, none; 1, very mild; 2, mild; 3, moderate; and 4, severe; Table 1] was used for each lesion. The scoring scale described the severity and/or the extent of the lesions across the following 10 body regions: head; neck; dorsal and lateral thorax; rump and tail; flanks; sternum and axillae; abdomen; perineum; forelimbs; and hindlimbs. If several lesion types were present, the sum of the scores was determined for each cat to

provide a total lesion score (TLS) ranging from zero to 16. To be eligible for inclusion, the TLS had to be two or more.

A visual analog scale (VAS) was used by owners to provide an Owner Pruritus Score (OPS) based on their cat's behaviour during the previous 3 days. The scale consisted of a line, which was marked at one end to indicate that the cat 'was comfortable, was grooming like any normal cat' and at the other end to indicate that the cat 'was uncomfortable, was grooming all the time'. For the investigators, a five-point numerical rating scale (Table 2) was used to provide an Investigator Pruritus Score (IPS) based on physical examination and interviewing the owner. Global Assessments of Improvement (GAI) using a numerical rating scale (Table 3) were made by both investigator and owner on day 21 (±3 days) and day 42 (±3 days).

For ethical reasons, cats considered as not responding to treatment and which had received the test material for at least 10 days could be withdrawn. At this stage, owners were given the option for their cat to be enrolled in a follow-up study, in which all cats would receive ciclosporin. Treatment acceptance was evaluated each day by the owner during dose administration.

Assessment of safety

In addition to full physical examination and body weight determination at each visit, blood samples were collected for haematology and biochemistry at inclusion and at study end, or in cases of premature withdrawal before day 42. Adverse events (AEs) were monitored by the owner and the investigator throughout the study. An AE was considered to be any observation that was unfavourable or unintended and occurred after the administration of either ciclosporin or placebo, whether or not considered to be related to treatment. All AEs, regardless of causality, were recorded during the study and assessed for causality prior to unblinding. Assessment of causality was made with the assumption that all cats received ciclosporin at a dose of 7.0 mg/kg.

Table 1. Lesion Severity Scale

Type of lesion	Score
Excoriations	0 = none 1 = very mild: small (≤1 cm long) erosion(s) in one body region 2 = mild: large (>1 cm long) erosion(s) in one body region, or small (≤1 cm long) erosion(s) in more than one body region 3 = moderate: large (>1 cm long) erosion(s) in more than one body region, or small (≤1 cm long) or large (>1 cm long) ulcer(s) in one body region 4 = severe: small (≤1 cm long) or large (>1 cm long) ulcer(s) in more than one body region
Miliary dermatitis	0 = none 1 = very mild: few (≤10) crusted papules in one body region 2 = mild: many (>10) crusted papules in one body region 3 = moderate: few (≤10) crusted papules in more than one body region 4 = severe: many (>10) crusted papules in more than one body region
Eosinophilic plaques	0 = none 1 = very mild: small (≤1 cm long) eroded plaque(s) in one body region 2 = mild: large (>1 cm long) eroded plaque(s) in one body region 3 = moderate: small (≤1 cm long) eroded plaques in more than one body region 4 = severe: large (>1 cm long) eroded plaques in more than one body region
Self-induced alopecia	0 = none 1 = very mild: one small (≤5 cm long) self-inflicted alopecic patch in one body region 2 = mild: one large (>5 cm long) self-inflicted alopecic patch in one body region, or more than one small (≤5 cm long) self-inflicted alopecic patch in one body region 3 = moderate: more than one large (>5 cm long) self-inflicted alopecic patch in one body region, or small (≤5 cm long) self-inflicted alopecic patches in more than one body region 4 = severe: large (>5 cm long) self-inflicted alopecic patches in more than one body region

Table 2. Investigator Pruritus Scale (IPS)

0 = the cat was comfortable, grooming like any normal cat
1 = the cat was grooming but it was tolerable and the cat remained calm
2 = the cat was grooming but it was generally tolerable
3 = the cat was grooming quite often, the cat was uncomfortable, nervous or often agitated
4 = the cat was uncomfortable, grooming all of the time

Table 3. Global Assessment Scale

0 = excellent (clinical signs observed during the first examination have completely disappeared)
1 = good (clear amelioration of the signs compared with initial examination)
2 = acceptable (clinical improvement compared with initial examination, but patient has responded only slightly to treatment)
3 = poor (clinical status of the cat compared with initial examination has not changed)
4 = bad (clinical status of the cat compared with initial examination has deteriorated)

Sample size

Sample size calculations, based on previously published studies, assuming that one lesion type would be present in most of the cats and that mean baseline scores would decrease by 14 and 45% on day 42 for the placebo and high-dose groups, respectively, indicated that at least 26 animals per group would be needed to obtain a significant difference at $P < 0.05$ with 80% power. The minimal sample size was therefore fixed at 30 cats per group.

Statistical analysis

Evaluation of efficacy was based on two primary variables, the numerical improvement of the TLS and the investigator GAI. Secondary variables were the owner GAI, the IPS and OPS, and the number of regions with lesions. Demographic and baseline data were compared between groups using the Mann–Whitney *U*-test for ordinal data or the Kruskal–Wallis test for nonbinary nominal data. Analysis of variance (ANOVA) methods were used to assess the efficacy data. Baseline values or demographic variables (e.g. age) were used as a covariate when appropriate. For multiple and bilateral group comparison, a repeated-measurements analysis of covariance (RMANCOVA) including both visits was used. The percentage improvements between visits were calculated as (initial – final score)/initial score × 100%.

Demographic and other baseline data were analysed on the per-protocol population at inclusion. The efficacy variables were analysed on an intent-to-treat (ITT) population. The ITT population was defined as all cats that were randomized to study and received at least one administration of the allocated test material. In the case of premature withdrawal, the missing values were replaced using the last value carry forward procedure. Significance was set at $P < 0.05$. All statistical analyses, including sample size calculation, were performed using SAS® Software, v9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 101 cats were randomized between March 2006 and February 2007, with recruitment evenly spread

between country centres and treatment groups. One cat did not receive any study medication because it was found to have a positive feline leukaemia virus titre, and was therefore disregarded for any further analysis. Of the remaining 100 cats included in the ITT analyses, there were 35, 32 and 33 cats in the placebo, low-dose and high-dose groups, respectively (Table 4). Most of the cats were domestic or European short hair cats (73 of 100). Ten pedigree breeds were represented (15 of 100), with the remainder (12 of 100) described as mixed breed and domestic medium or long hair. There were no statistically significant differences at baseline for any of the demographic factors (Table 4).

Clinical characteristics for the primary and secondary variables are summarized in Tables 5 and 6. All three treatment groups had similar TLSs at baseline ($P = 0.7330$), with an overall mean of 7.2 ± 3.4, and all lesion types contributed to the TLS.

The investigators classified pruritus as moderate or severe (score of 3 or 4) in 69% of the cats (mean IPS 2.8 ± 0.9). Pruritus evaluation by the owners was similar, with 68% of the cats given scores of 60–100 (mean OPS 67 ± 23). There was no significant difference between groups in either IPS or OPS at inclusion (Table 6).

At inclusion, SA was the most frequently reported lesion type (85%), followed by E (77%), MD (48%) and EP (46%). The mean (±SD) baseline lesion scores were 2.8 (±1.5) for SA, 1.9 (±1.3) for E, 1.3 (±1.6) for MD and 1.2 (±1.6) for EP. All lesion types were evenly distributed among treatment groups, with no significant differences between groups for any lesion type ($P > 0.1301$). Two or more lesion types were observed in 69% of cats. The simultaneous presence at baseline of two, three or four lesion types was noted in 38, 21 and 10% of the cats, respectively. In the majority of cats, lesions were distributed over several body regions, and only 18% of cats had lesions in one region only. Thirty-six per cent of the cats had lesions in two or three regions, 28% had lesions distributed over four to six regions, and 18% had lesions present in seven or more body regions.

Table 5. Primary efficacy variables

Response variable	Time	Placebo ($n = 35$)	Low dose ($n = 32$)	High dose ($n = 33$)	P-value*
TLS	Day 0	7.2 ± 3.6	6.8 ± 2.8	7.7 ± 3.9	0.7330
	Day 42	5.6 ± 3.6	4.5 ± 3.8	2.9 ± 2.7	0.0003
Investigator GAI	Day 42	2.5 ± 1.3	1.8 ± 1.5†	1.4 ± 1.4	0.0012
Individual TLS Improvement >50%	Day 42	8 (23)	15 (47)	23 (70)	0.0006

Abbreviations: GAI, Global Assessment of Improvement; and TLS, Total Lesion Score. Values for TLS and investigator GAI are given as means ± SD, while improvement in TLS is given as n (%).
*Day 42 P-values are for high dose compared with placebo.
†$n = 30$ because no data were available for two cases.

Table 6. Secondary end-points

Response variable	Time	Placebo ($n = 35$)	Low dose ($n = 32$)	High dose ($n = 33$)	P-value*
No. of regions with lesions (mean ± SD)	Day 0	3.7 ± 2.8	3.8 ± 1.8	3.9 ± 2.3	0.6779
	Day 42	3.0 ± 2.3	2.6 ± 2.5	1.6 ± 1.4	0.0017
IPS (mean ± SD)	Day 0	2.8 ± 0.9	2.8 ± 0.8	2.8 ± 0.9	0.9747
	Day 42	2.2 ± 1.3	1.9 ± 1.5	1.3 ± 1.4	0.0063
OPS (mean ± SD)	Day 0	65 ± 24	69 ± 23	66 ± 21	0.6727
	Day 42	54 ± 33	46 ± 36	31 ± 30	0.0046
Owner GAI (mean ± SD)	Day 42	2.5 ± 1.3	1.7 ± 1.6†	1.3 ± 1.2‡	0.0039

Abbreviations: GAI, Global Assessments of Improvement; IPS, Investigator Pruritus Score; and OPS, Owner Pruritus Score.
*Day 42 P-values are for high dose compared with placebo.
†$n = 30$ because no data were available for two cases.
‡$n = 32$ because no data were available for one case.

Participant flow

Twenty-eight cats did not complete the study, as follows: 12 of 35 (34%) in the placebo group; 12 of 32 (38%) in the low-dose group; and four of 33 (12%) in the high-dose group. No cat was withdrawn before day 10. Thirty-eight per cent of withdrawals occurred between days 10 and 14, 50% from day 15 to 31, and the remaining 12% between day 32 and study end. Significantly more cats failed to complete the study in the placebo and low-dose groups than in the high-dose group ($P = 0.0454$). Lack of efficacy was the most frequent reason for premature withdrawal, cited in 11 of 12, nine of 12 and two of four cats withdrawn from the placebo, low-dose and high-dose groups, respectively. Adverse effects were cited in only two cases, both from the low-dose group, one of which was anorexic, leading to withdrawal of owner consent, whereas the other was in fact withdrawn for lack of efficacy reasons, but the investigator indicated this to be an AE. Other reasons for withdrawal included owner request (two cases in placebo and low-dose groups), lack of compliance (one case in the high-dose group) and medication not taken by the cat (one case in the high-dose group).

Table 4 . Baseline characteristics of the intent-to-treat population

Demographic	Placebo ($n = 35$)	Low dose ($n = 32$)	High dose ($n = 33$)	P-value
Age (years)	6.6 ± 3.6	5.5 ± 3.7*	7.1 ± 3.8	0.17
Weight (kg)	5.3 ± 1.8	5.0 ± 1.4	5.1 ± 1.1	0.71
Males	16 (46%)	14 (44%)	16 (48%)	0.93
Indoor only	21 (60%)	19 (59%)	22 (67%)	0.65
Urban	30 (86%)	26 (81%)	29 (88%)	0.61

Age and weight are given as means ± SD; other variables are given as n (%).
*$n = 31$ because no data were available for one case.

Acceptance

During the first 3 weeks, treatment was given with food in 69, 52 and 39% of the cats in the placebo, low-dose and high-dose group, respectively. The numbers were similar in the second 3 weeks, being 73, 55 and 36%, respectively. This indicates that the high-dose treatment was primarily administered directly into the mouth ($P = 0.0005$ and 0.0244 compared with the placebo and low-dose group, respectively). Medicated food was eaten almost completely by approximately 90% of the cats. Compliance with treatment was generally good, with only one cat (from the high-dose group) withdrawn because it was not possible to administer medication.

Primary efficacy assessments

A summary of the primary end-point assessments is presented in Table 5, and the change of TLS over time is shown on Figure 1. The high-dose group had a significantly greater improvement in mean TLS, from 7.7 to 2.9 compared with from 6.8 to 4.5 in the low-dose group and from 7.2 to 5.6 in the placebo group ($P = 0.0047$ and $P = 0.0003$, respectively). This was equivalent to a mean percentage improvement of 62, 34 and 23% in the high-dose, low-dose and placebo group, respectively. At day 42, furthermore, the TLS of individual cats had improved by more than 50% in 23 of 33 (70%) in the high-dose group, compared with eight of 35 (23%) in the placebo group and 15 of 32 (47%) in the low-dose group ($P = 0.0006$). In addition, the proportion of cats with severe lesions (TLS > 6) at the final visit was lower in the high-dose group (from 52% on day 0 to 15% on day 42) compared with the low-dose (from 56% on day 0 to 38% on day 42) and placebo groups (from 51% on day 0 to 44% on day 42; $P = 0.0105$). There were no significant differences between the low-dose and placebo groups for any of these parameters.

There was also a statistically significant improvement in the investigators' GAI scores for both the high-dose and low-dose groups compared with the placebo group ($P = 0.0012$ and $P = 0.0465$, respectively; Table 5). At day 42, the response was described as excellent or good in 20 of 33 (61%) cats in the high-dose group, compared with 14 of 30 (47%; two cases had missing values) in the low-dose group and eight of 35 (23%) in the placebo group. Conversely, the cat's condition deteriorated in eight of 35 (23%) in the placebo group and six of 30 (20%) in the low-dose group, compared with only three of 33 (9%) in the high-dose group. The difference between groups regarding the distribution of the GAI scores was significant for the high-dose versus placebo and low-dose versus placebo groups (ANCOVA test, $P = 0.0009$ and 0.044, respectively).

Secondary efficacy assessments

The secondary efficacy variables are summarized in Table 6. There was a 58% reduction in the number of regions with lesions in the high-dose group, compared with 30% in the low-dose group and only 18% in the placebo group ($P = 0.0180$ and $P = 0.0017$, respectively). There was no significant difference observed between the low-dose and the placebo groups.

There was a significantly greater improvement in IPS scores in the high-dose group (54%) at day 42 compared with the low-dose (32%) and placebo groups (21%; $P = 0.0232$ and 0.0063, respectively). Moreover, the investigators reported that 21 of 33 (64%) cats in the high-dose group were comfortable or calm, with a tolerable level of grooming (score '0' or '1'), compared with 13 of 32 (41%) in the low-dose group and 12 of 35 (34%) in the placebo group.

The mean improvements in OPS were 53% in the high-dose group, 33% in the low-dose group and 17% in the placebo group (Figure 2) at day 42. The improvement in OPS was significant for the high-dose group compared with the placebo group ($P = 0.0046$). The OPS improved by more than 50% in 21 of 33 (64%) cats in the high-dose group compared with 13 of 32 (41%) in the low-dose group and only eight of 35 (23%) in the placebo group ($P = 0.0032$).

The owner GAI scores were excellent or good in 19 of 32 (59%) cats in the high-dose group compared with 15 of 30 (50%; two cases had missing values) in the low-dose and eight of 35 (22%) in the placebo groups. Similar to the investigator GAI, owners felt that seven of 35 (20%) cats in the placebo group and six of 30 (20%) in the low-dose group deteriorated, compared with only one of 32 (3%) in the high-dose group. The owner GAI scores were significantly in favour of the high dose compared with the placebo group ($P = 0.0039$).

The percentage improvement over baseline for each of the four individual lesion patterns is shown in Figure 3. In the high-dose group, all four lesion patterns showed a > 50% improvement. In the low-dose group, the improvement ranged from 33% for MD to 52% for EP, and in the placebo group the improvement ranged from only 7% for SA to 44% for MD. The improvements in the individual lesion scores were significantly greater in the

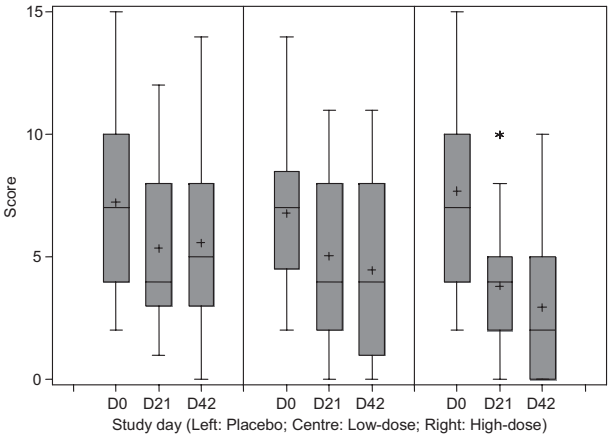

Figure 1. Change in Total Lesion Score over time. Each box goes from the lower quartile, with a horizontal line at the median and a cross at the mean; whiskers extend from the minimum to the maximum. 'Far values' (more than 1.5 times the interquartile distance away from the box), are displayed as asterisks.

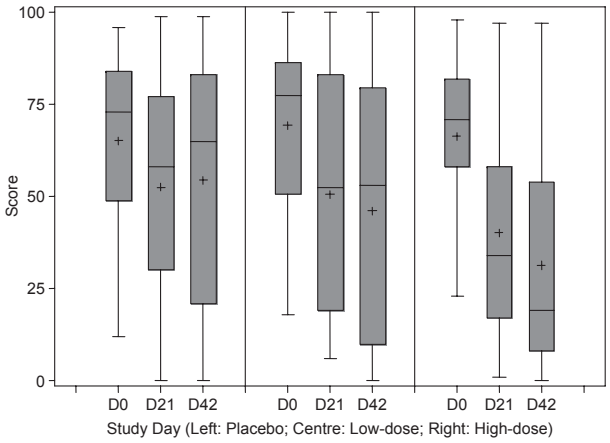

Figure 2. Change in Owner Pruritus Score (visual analog scale) over time. Each box goes from the lower quartile, with a horizontal line at the median and a cross at the mean; whiskers extend from the minimum to the maximum.

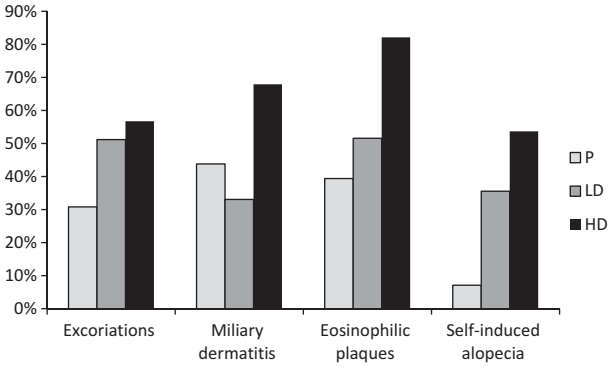

Figure 3. Percentage improvement in individual lesion types at day 42 in cats.

high-dose compared with the low-dose and placebo groups ($P < 0.05$) for all lesion patterns except MD.

Safety assessment

There was no age-, breed- or sex-related pattern to the reporting of AEs. One hundred and thirteen AEs were described, but the majority were mild or moderate and the cats completely recovered without withdrawing study medication. Eighteen AEs were considered clinically significant (i.e. moderate to severe and may have required medical intervention). Of these, eight (in six cats) were in the high-dose group, seven (five cats) were in the low-dose group and three (three cats) were in the placebo group. Observed AEs were primarily digestive tract disorders, including vomiting, diarrhoea and hypersalivation. Vomiting was seen in 11, 12 and seven cats in the high-dose, low-dose and placebo group, respectively. Vomiting occurred periodically or on more than one occasion in five, six and seven cats in these respective treatment groups.

After digestive tract disorders, the next most common group of AEs were the miscellaneous topical and systemic disorders, which included test results outside normal reference ranges (regardless of association with clinical signs), lethargy, anorexia and loss of condition. A nonsignificant trend towards weight loss was seen in all groups during the first 3 weeks of the study, but this was reversed in the second 3 weeks.

Blood samples collected from two cats at study conclusion were seropositive (IgM titres of 1:64 and 1:128) for *Toxoplasma*. These cats were seronegative at inclusion and therefore developed these positive titres during the course of the study. Only one of these cats was in the 7.0 mg/kg dose group, while the other had received the placebo. Neither cat developed clinical signs of toxoplasmosis during the study.

Although within normal ranges, a statistically significant reduction ($P = 0.0020$) in the mean total white blood cell counts was observed in the high-dose group compared with the placebo group, but not in the low-dose group. The white blood cell differential cell counts showed that mean neutrophil counts were significantly reduced in the high-dose group compared with the placebo group ($P = 0.0102$), but this was still within normal reference ranges, and was not significantly different from baseline ($P = 0.1208$). Mean absolute eosinophil counts were also significantly lower in both ciclosporin treatment groups ($P \leq 0.0033$) compared with the placebo group, and in the high-dose group only significantly lower than at baseline ($P = 0.0248$). However, in both ciclosporin treatment groups, the mean eosinophil count was within the normal reference range, whereas in placebo-treated cats it was higher than normal.

An evaluation of clinical chemistry parameters indicated a small but statistically significant elevation in total bilirubin ($P = 0.0083$, compared with placebo), glucose ($P = 0.0108$, compared with placebo; $P = 0.0008$, compared with low dose) and urea ($P = 0.0424$, compared with placebo; $P = 0.0374$, compared with low dose) in the high-dose group of cats. However, the reported values were all within normal reference ranges, and no changes were seen in creatinine levels in any group.

Concomitant medications

Antibiotics were administered to two of 35, five of 32 and five of 33 cats in the placebo, low-dose and high-dose group, respectively. Antifungal agents were given to only one cat each in the low-dose and high-dose groups. The same applied to the use of shampoos. An Elizabethan collar was utilized at study initiation (up to 10 days) for highly pruritic cats in four of 35, four of 32 and one of 33 cases in the placebo, low-dose and high-dose group, respectively.

Discussion

Very few blinded randomized placebo-controlled clinical studies have been performed to assess the response to therapies intended to treat dermatological conditions in cats. The efficacy and safety of corticosteroids and antihistamines, commonly recommended in the treatment of feline HD, have not been evaluated in well-controlled clinical trials. Dose and treatment regimens based on clinical observations remain somewhat controversial.[12] This blinded randomized study was designed to establish an effective dose for ciclosporin for the treatment of feline HD with cats in Europe and USA, in various environmental conditions. The three groups showed very similar demographic and disease severity characteristics at baseline, indicating that randomization was adequate and that inclusion bias was unlikely.

This study clearly demonstrates that administration of ciclosporin at 7.0 mg/kg once daily led to a significant improvement in TLS, extent of lesions and pruritus, which were correlated with clinical improvement as assessed by both the investigator's and owner's GAI. There was little improvement, in contrast, in the 2.5 mg/kg once daily ciclosporin and placebo groups. These results confirm the published literature, which shows that ciclosporin in the range of 5–10 mg/kg daily is efficacious in the treatment of a variety of feline allergic skin diseases.[9–11] The dose of 7.0 mg/kg once daily is slightly higher than the dose recommended in dogs (5.0 mg/kg once daily) for the treatment of atopic dermatitis. However, ciclosporin pharmacokinetics in cats are more variable than in dogs.[13] The bioavailability may be lower in some individuals, which may therefore require a slightly higher dose.

The severity of pruritus may not have been fully reflected in the owner VAS, because it measured grooming behaviour and potentially ignored other signs of pruritus, such as licking and scratching, which some owners may not have identified as grooming behaviour. However, the change of pruritus severity paralleled the change of the TLS, indicating that these two independent measures were consistently assessing the disease severity. In addition, the IPS combined information given by the owner on the cat behaviour and the physical observations made at the time of the cat examination. Like the VAS, the IPS change over time paralleled the change of the TLS.

Concomitant medications administered during the study, such as antibiotics, antifungal agents or shampoos, and the use of an Elizabethan collar at study initiation (up to 10 days) may have influenced the study outcome; however, their impact appears limited. Use of these concomitant medications occurred in all groups with a low and similar frequency, and for limited durations.

Cats received a monthly flea adulticide treatment for the duration of the study except in US regions not considered flea endemic. However, even in such regions a low flea population could still be present during the study. The lack of flea prevention in these areas probably had little influence on the study outcome, because the study was multi-centered with a large number of sites and with no more than 11 cases enrolled in a flea-free area.

The study was not designed or powered to test the treatment effect on the different individual types of lesions present in feline HD. However, exploratory analysis showed that SA, EP and E trended towards significant improvement in the high-dose group more than in the other treatment groups. The degree of improvement over baseline was highest for EP. The SA lesions also improved by slightly more than 50% in the high-dose group, whereas there was hardly any improvement in the placebo group cats. Miliary dermatitis was the only lesion type where no statistically significant difference was found, but it is likely that this was due to the higher improvement rate in the placebo group rather than lack of efficacy in the ciclosporin group.

The TLS of the cats that received placebo improved by 23% in the absence of any systematic intervention other than the administration of a monthly flea adulticide. Reduction of flea infestation is unlikely to be the reason for this spontaneous clinical improvement, because cats were only included in the study after exclusion of flea-bite hypersensitivity, through the use of a flea adulticide treatment, with no clear improvement of the lesions. Two cats from the placebo group received antibiotics, which is unlikely to have significantly influenced the mean response. Lesions of eosinophilic plaque may improve with antibiotic treatment,[14] but eosinophilic plaque represented only a small proportion of all the lesions that were observed. It is still possible that the initial use of an Elizabethan collar in four cats may have contributed to the improvement in the early phase of the study. The improvement in TLS in the placebo-treated cats is in the same range as previously described for atopic dogs in similar clinical trials,[15] highlighting the importance of randomized controlled trials.

Clinical assessment of the lesions was based on a categorical score specifically designed to measure the severity and the extent of individual types of lesions. A score similar to the CADESI score did not appear to be appropriate, although it has been validated[16] and previously adapted for cats in pilot studies.[9,11] The lesions observed in cats with feline HD are very diverse, making it difficult to use the same criteria in the presence of SA, E, EP or MD. As the repeatability of the score had not been previously verified, all cats were scored by the same investigators. Interobserver variability was not measured, but the large number of investigators in this study and the even distribution of cases among them reduces the chance of an investigator effect that could have biased the study outcome. A separate analysis has validated the utility of the scoring scale as an outcome measure in feline HD and has defined thresholds for clinical success.[17]

Owing to the absence of any standardized and validated clinical end-point in earlier studies, it was not possible to establish *a priori* criteria for a clinically significant improvement. The improvements in TLS and pruritus, however, were highly correlated with the GAI scores from the investigator and the owner; for example, following 7.0 mg/kg ciclosporin there was a >50% mean improvement in TLS and pruritus and the GAI was excellent or good in 61% of cats.[17] This suggests that, as in dogs,[18] improvements of 50% or more in pruritus and clinical lesions are clinically significant. However, the relative importance of pruritus and lesions in the overall assessment of the response in cats with different lesion types remains unclear. Further analysis of the associations between lesions, pruritus and global assessment is needed to establish the most critical end-points and thresholds for defining a clinically significant response.

A complete lack of response or an inadequate response was observed in 9 and 15%, respectively, of cats in the high-dose group. There was no evidence that a poor response was associated with a specific lesion type. Most cats enrolled in the study had a long history of hypersensitivity dermatitis, which had not responded to other treatments. Thus, these cats may have been more recalcitrant to treatment than the general hypersensitivity dermatitis population. Nevertheless, the number of poor responders was lower than in another blinded study,[11] which reported that prednisolone failed to improve lesion scores by more than 25% in the majority of treated cats.

As in dogs, the most frequent AEs associated with ciclosporin treatment were gastrointestinal, mostly transient vomiting and diarrhoea. These were only slightly more frequent in the ciclosporin-treated cats than in the placebo group. Biochemistry did not reveal any signs of hepatic or renal toxicity, as has been previously reported at a higher dose of 20 mg/kg.[19] The only significant change in haematology was a reduction in white blood cell counts, notably eosinophils, as noted by Nakazato *et al.*[20] This is probably due to the pharmacological activity of ciclosporin, and eosinophil inhibition is likely to be associated with therapeutic efficacy in these skin conditions, which is supported by the control group having eosinophil counts that were above the upper limit of the normal range. Although neutrophil counts were reduced with high-dose ciclosporin treatment, they remained within normal ranges. The observed reduction in neutrophil counts may also have been attributed to better control in

the upregulation of inflammation of ciclosporin-treated cats. The observed weight loss in the first 3 weeks of the study was thought to be due to reduced palatability of the medicated food. The weight loss was reversed over the last 3 weeks of the trial, when most cats were medicated directly. The efficacy was similar whether the medication was administered with food or directly into the mouth (data not shown).

In conclusion, this study has established that 7.0 mg/kg ciclosporin once daily is efficacious and well tolerated in the treatment of feline HD. Further studies are needed to assess the clinical response and safety in larger cat populations and for longer treatment durations.

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Résumé

Contexte – Les dermatites par hypersensibilité (HD) sont fréquemment suspectées chez les chats mais peu d'études cliniques existent dans la littérature sur les traitements sûrs et efficaces.

Objectifs – Etablir une dose sure et efficace de cyclosporine dans le traitement des HD félines.

Sujets – Cent propriétaires de chats atteints de HD féline.

Méthodes – Une étude en double aveugle dont les chats sont désignés au hasard pour recevoir de la cyclosporine à 7.0 mg/kg une fois par jour (n = 33) ou à 2.5 mg/kg une fois par jour (n = 32) ou un placebo (n = 35) pendant 6 semaines.

Résultats – Les scores de lésion totaux moyens avec 7.0 mg/kg de cyclosporine étaient significativement plus faibles qu'avec 2.5 mg/kg de cyclosporine ($P = 0.0047$) ou le placebo ($P = 0.0003$) à la fin de l'étude. Les scores lésionnels totaux individuels se sont améliorés de plus de 50% pour 70% du groupe à 7.0 mg/kg comparé avec 47% dans le groupe à 2.5 mg/kg et 23% dans le groupe placebo ($P = 0.0006$). L'évaluation globale de l'amélioration des investigateurs était « excellent » ou « bon » pour 61% des chats traités à 7.0 mg/kg de cyclosporine, comparé à 47% des chats recevant 2.5 mg/kg et 23% des chats recevant le placebo. L'amélioration des scores de prurit des investigateurs était significativement meilleur chez les chats traités avec 7.0 mg/kg de cyclosporine (54%) comparé à la fois avec 2.5 mg/kg de cyclosporine (32%; $P = 0.0232$) et le placebo (21%; $P = 0.0063$). Des troubles gastro-intestinaux modérés étaient les effets secondaires les plus fréquents et ne nécessitaient pas l'arrêt du traitement.

Conclusion et importance clinique – Ces résultats suggèrent que la cyclosporine à la dose de 7.0 mg/kg de cyclosporine une fois par jour dans la nourriture ou per os pendant 6 semaines est efficace et bien toléré dans les cas d'HD félines.

Resumen

Introduccion – la dermatitis por hipersensibilidad (HD) se sospecha con frecuencia en gatos, pero hay pocos estudios clínicos publicados con tratamientos seguros y eficaces.
Objetivos – establecer una dosis segura y efectiva de ciclosporina en el tratamiento de la HD felina.
Animales – cien gatos de propietarios particulares con HD felina.
Métodos – estudio doble ciego, con gatos asignados al azar para recibir ciclosporina una vez al día a dosis de 7,0 mg/kg (n = 33) o de 2,5 mg/kg (n = 32) o bien placebo (n = 35) durante 6 semanas.
Resultados – los valores totales de las lesiones en gatos tratados con 7,0 mg/kg fueron significativamente más bajos que en animales tratados con ciclosporina a dosis de 2,5 mg/kg (P = 0,0047) o placebo (P = 0,0003) al final del estudio. Las valores totales individuales de lesiones mejoraron en >50% en un 70% de gatos en el grupo de 7,0 mg/kg, comparado con un 47% en el grupo de 2,5 mg/kg y un 23% en el grupo placebo (P = 0,0006). La valoración global de la mejora por parte de los investigadores se consideró excelente o buena en un 61% de gatos tratados con ciclosporina a 7,0 mg/kg, comparado con un 47% de gatos tratados con 2,5 mg/kg y un 23% en gatos administrados con placebo. La mejora en la valoración del prurito por el investigador fue significativamente mayor en gatos tratados con ciclosporina a 7,0 mg/kg (54%) comparado con el tratamiento de ciclosporina a 2,5 mg/kg (32%; P = 0,0232) y placebo (21%; P = 0,0063). Las reacciones adversas mas comunes fueron alteraciones gastrointestinales ligeras, las cuales no necesitaron interrupción del tratamiento.
Conclusiones e importancia clínica – los resultados sugieren que el uso una vez al día de ciclosporina a dosis de 7,0 mg/kg en el alimento o por vía oral durante 6 semanas es eficaz y bien tolerado en el tratamiento de la HD felina.

Zusammenfassung

Hintergrund – Hypersensibilitätsdermatitiden (HD) werden bei Katzen häufig vermutet, aber in diversen Veröffentlichungen findet man nur wenige klinische Studien über sichere und wirksame Behandlungen.
Ziele – Ermittlung einer sicheren und wirksamen Dosis für die Behandlung von feliner HD mit Ciclosporin.
Tiere – einhundert private Katzen mit feliner HD.
Methoden – Eine doppelblinde Studie, bei der die Katzen zufällig eingeteilt wurden, um Ciclosporin mit einer Dosis von entweder 7,0 mg/kg einmal täglich (n = 33) oder 2,5mg/kg einmal täglich (n = 32) oder ein Plazebo (n = 35) 6 Wochen lang verabreicht zu bekommen.
Ergebnisse – Die durchschnittlichen ,,Läsionsgrade'' lagen zu Studienende bei 7,0 mg/kg Ciclosporin signifikant niedriger als bei 2,5 mg/kg Ciclosporin (P = 0,0047) oder bei Verabreichung von Plazebo (P = 0,0003). Die individuellen Gesamtwerte der ,,Läsionsgrade'' verbesserten sich zu >50% bei 70% der 7,0 mg/kg Gruppe, im Vergleich zu 47% der 2,5 mg/kg Gruppe und 23% der Plazebogruppe (P = 0,0006). Die Gesamtbeurteilung wurde von den UntersucherInnen bei 61% der Katzen, die mit 7,0 mg/kg Ciclosporin behandelt worden waren, als ,,exzellent'' oder ,,gut'' eingestuft, im Vergleich zu 47% der Katzen, denen 2,5mg/kg und 23% der Katzen, denen Plazebo verabreicht worden war. Die Verbesserung der Bewertung des Pruritus durch die UntersucherInnen war bei Katzen, die mit 7,0 mg/kg Ciclosporin (54%) behandelt worden waren, signifikant besser als bei Katzen, die mit 2,5 mg/kg Ciclosporin (32%; P = 0,0232) sowie auch bei jenen, die mit Plazebo (21%; P = 0,0063) behandelt worden waren. Milde gastrointestinale Störungen waren die häufigsten Nebenwirkungen, wobei diese aber nicht eine frühzeitige Beendigung der Behandlung erforderlich machten.
Schlussfolgerung und klinische Bedeutung – Die Ergebnisse weisen darauf hin, dass die Behandlung mit 7,0 mg/kg Ciclosporin einmal täglich mit dem Futter oder *per os* für 6 Wochen für die feline HD wirksam ist und auch gut vertragen wird.

要約

背景 – 過敏性皮膚炎（HD）は猫で頻繁に疑われる、しかし安全で効果的な治療法についての臨床試験の報告は少ない。

目的 – 猫のHDの治療に安全で有効なシクロスポリン用量を確立する。

供与動物 – 猫HDの飼い猫100頭

方法 – 二重盲検試験にて、猫をシクロスポリン7.0mg/kg1日1回（n = 33)、2.5 mg/kg 1日1 回(n = 32)あるいはプラセボ(n = 35)に無作為に割り付け，6 週間投与した。

結果 – 7.0 mg/kg シクロスポリン群の平均総病変スコア （MTLS） は試験終了時に 2.5 mg/kg シクロスポリン群（P = 0.0047）およびプラセボ群（P = 0.0003)に比べて有意に低かった。総病変スコアの 50% 以上改善率は 2.5 mg/kg 群では 47%，プラセボ群では 23% と 比較し、7.0 mg/kg 群では 70% であった(P = 0.0006)。研究者による総合改善度評価は 2.5 mg/kg 群の 47%，プラセボ群の 23% が ‘極めて有効’または‘有効’であったのに対し、7.0 mg/kg 群では 61% で‘極めて有効’または‘有効’と評価された。研究者による瘙痒スコア改善度は，7.0 mg/kg 群では 54% であり，2.5 mg/kg 群(32%; P = 0.0232)やプラセボ群(21%; P = 0.0063)と比較し有意に高かった。軽度の胃腸障害が最も一般的な有害事象であったが、治療の中止は必要でなかった。

結論と臨床的な重要性 – 7.0 mg/kg のシクロスポリンを1日１回，6 週間，食事とともに、あるいは経口投与は，猫のHDに有効で，耐性のあることを示していた。

摘要

背景 – 猫常被怀疑过敏性皮炎（HD），但在已发表的文献上，很少有治疗安全性和功效的临床研究。

目的 – 确定环孢素治疗猫HD的安全和有效剂量。

动物 – 一百只家养HD患猫。

方法 – 双盲研究，猫随机分配接受环孢素 7.0 mg/kg 每日一次（n =33）或 2.5 mg/kg 每日一次（n=32）或安慰剂（n = 35）治疗六周。

结果 – 在研究结束时，环孢素 7.0 mg/kg 组的平均病变评分显著低于环孢素 2.5 mg/kg 组（P =0.0047）或安慰剂组（P = 0.0003）。个体病变评分改善> 50% 的百分比， 7.0 mg/kg 组为 70%，2.5 mg/kg 组 47% 和安慰剂组 23%（P = 0.0006)。改善的整体评估中研究者给出的“非常好”或“好”的评定，在给予环孢素 7.0 mg/kg治疗的猫是 61%，给予 2.5 mg/kg 的猫为 47% 和给予安慰剂的猫为 23%。7.0 mg/kg 环孢素治疗猫（54%）与 2.5 mg/kg 环孢素组（32%; P = 0.0232）和安慰剂组（21%; P = 0.0063）相比，研究者瘙痒评分的改善显著大于两者。轻度胃肠道功能紊乱是常见的不良反应，但无需因此终止治疗。

结论和临床价值 – 结果表明环孢素 7.0 mg/kg 每日一次，伴随食物或直接口服，持续六周治疗猫HD有效，而且耐受性良好。