Veterinary Dermatology

Vet Dermatol 2015; **26**: 23–e8 DOI: 10.1111/vde.12186

A blinded, randomized clinical trial comparing the efficacy and safety of oclacitinib and ciclosporin for the control of atopic dermatitis in client-owned dogs

Peter R. Little*, Vickie L. King†, Kylie R. Davis*, Sallie B. Cosgrove† and Michael R. Stegemann‡

*Veterinary Medicine Research and Development, Zoetis, 45 Poplar Road, Parkville, VIC, 3052, Australia
†Veterinary Medicine Research and Development, Zoetis, 333 Portage Street, Kalamazoo, MI, 49007, USA
‡Veterinary Medicine Research and Development, Zoetis, Mercuriusstraat 20, 1930, Zaventem, Belgium

Correspondence: Peter R. Little, Veterinary Medicine Research and Development, Zoetis, 45 Poplar Road, Parkville, VIC 3052, Australia.
E-mail: peter.little@zoetis.com

Background – Ciclosporin is approved for the treatment of atopic dermatitis (AD) in dogs and has been shown to be safe and effective. Placebo-controlled studies suggest that oclacitinib is a safe and effective alternative therapy.

Hypothesis/Objectives – To evaluate the efficacy and safety of oclacitinib, in comparison to ciclosporin, for the control of AD in a blinded, randomized clinical trial, incorporating a noninferiority test at day 28.

Animals – A total of 226 client-owned dogs with a history of AD from eight sites were enrolled.

Methods – Enrolled animals were randomized to receive oral oclacitinib (0.4–0.6 mg/kg twice daily for 14 days, then once daily) or oral ciclosporin (3.2–6.6 mg/kg once daily) for 12 weeks. Owners assessed pruritus using an enhanced visual analog scale (VAS), and veterinarians assessed dermatitis using the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-02.

Results – On days 1, 2, 7, 14, 28, 56 and 84, the percentage reduction from baseline for owner-assessed pruritus changed from 25.6 to 61.0% in the oclacitinib group compared with 6.5 to 61.5% in the ciclosporin group; differences were significant at all time points up to day 28. On day 56, ciclosporin-treated dogs showed a similar decrease in pruritus to oclacitinib-treated dogs. On day 14, the percentage reduction from baseline CADESI-02 was significantly greater in the oclacitinib group (58.7%) than in the ciclosporin group (43.0%). Three times as many adverse events attributed to gastrointestinal signs were reported in the ciclosporin group compared with the oclacitinib group.

Conclusions and clinical importance – In this study of treatment for canine AD, oclacitinib had a faster onset of action and a lower frequency of gastrointestinal side effects compared with ciclosporin.

Introduction

Atopic dermatitis (AD) is a common chronic allergic skin disease in dogs that involves environmental allergens; pruritus associated with canine AD is a frequent presenting complaint in general and referral veterinary practice.[1] Canine AD is a multifactorial condition that involves cutaneous dendritic cells, T lymphocytes, a multiplicity of other cells and an altered skin barrier function at the centre of the disease process.[2] Environmental allergens that penetrate the cutaneous barrier trigger a complex immunological reaction involving the release of many different cytokines that drive the process, resulting in cutaneous inflammation and neuronal mechanisms that initiate the never-ending cycle of pruritus.[2]

Guidelines for the management of canine AD have been produced by the International Committee for Allergic Diseases of Animals (ICADA).[3] The most effective treatments based on systematic reviews are as follows: anti-inflammatory agents, including topical and oral glucocorticoids, oral ciclosporin and topical tacrolimus; antimicrobial therapy to manage secondary bacterial or fungal infections; bathing with nonirritating shampoos; and allergen-specific immunotherapy.[3–5] There is no universal treatment protocol, and the management of canine AD needs to be tailored to the individual case based on response to therapy, potential for adverse effects, owner compliance and medication costs.

Ciclosporin (Atopica®; Novartis Animal Health Australasia Pty Ltd, North Ryde, NSW, Australia) is approved for the treatment of canine AD at a daily dose of 5 mg/kg p.o. (range 3.1–6.7 mg/kg p.o.).[6] There is good evidence for the efficacy of oral ciclosporin and it may take 4–6 weeks to achieve satisfactory clinical improve-

Accepted 19 August 2014
Sources of Funding: This study was initiated and funded by Pfizer Animal Health; final stages of the study were funded by Zoetis Inc.
Conflict of Interest: All authors are current or former employees of Zoetis (formerly Pfizer Animal Health).

ment.[4,7,8] Gastrointestinal side effects may be observed; in a systematic review of clinical trials involving ciclosporin, vomiting and diarrhoea were reported with an overall prevalence of 25 and 15%, respectively.[7]

The Janus kinase (JAK) inhibitor, oclacitinib (Apoquel®; Zoetis Inc., Florham Park, NJ, USA), is approved in a number of countries for the control/treatment of pruritus associated with allergic dermatitis and the control/treatment of AD in dogs >12 months of age.[9,10] Oclacitinib is a targeted therapy that selectively inhibits key pathways that lead to itch stimulation and cutaneous inflammation, particularly through the inhibition of JAK-1 signalling of interleukin-31, a cytokine shown to induce pruritus in dogs.[11–13] The efficacy and safety of oclacitinib have been demonstrated in placebo-controlled, randomized clinical trials in client-owned dogs.[14,15] The present study was conducted to investigate the efficacy and safety of oclacitinib in comparison to ciclosporin for the control of AD in dogs, in a randomized clinical trial.

Materials and methods

Overview

Seven study investigators enrolled a total of 226 client-owned dogs with a history of chronic, nonseasonal AD in an 84 day study. The study was conducted in compliance with applicable animal welfare regulations relating to the care and use of animals for scientific purposes, and the study protocol was approved by the relevant institutional Animal Ethics Committee. The study was conducted in accordance with good clinical practice guidelines,[16] and written informed consent was obtained from the owner of each participating dog. Many of the methods used in this study, particularly inclusion criteria, exclusion criteria and excluded and conditionally allowed concurrent medications (including drug withdrawal times), were as previously reported;[15] a summary of methods and key differences are provided here.

Study design and sample size estimation

This study was conducted as a positively controlled, single-blinded clinical trial with a randomized complete block design, replicated at eight study sites in Australia. The individual animal was the experimental unit, and blocking was based on the order of enrolment at each clinic. The intended period of study for each enrolled dog was 84 ± 2 days. Ciclosporin was used as the positive control drug. The primary measures of efficacy were the percentage reduction from baseline for both owner-assessed pruritus and investigator-assessed Canine Atopic Dermatitis Extent and Severity Index (CADESI)-02, each incorporating a noninferiority test at day 28. Using a noninferiority margin of 15% and a one-sided significance level of 0.05, a sample size of 99 animals per treatment was required to show noninferiority of oclacitinib compared with ciclosporin for CADESI-02, with 80% power.

Inclusion and exclusion criteria

All dogs enrolled were to be >12 months of age, weigh between 3 and 80 kg, have moderate to severe pruritus (owner assessed) using a categorical scale and a minimum CADESI-02 score (investigator assessed) of 25 of a possible 360 points. Systemic azole antifungals (e.g. ketoconazole) were prohibited in this study in order to avoid any potential influence on the pharmacokinetics of ciclosporin.

Randomization and blinding

Dogs meeting the inclusion criteria and relevant drug withdrawal times for excluded treatments were randomized in a 1:1 ratio to receive either oclacitinib or ciclosporin. A randomization file was produced for each study site using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). One or more nonblinded treatment dispensers at each study site allocated enrolled dogs to treatment groups, dispensed the trial medication and provided instructions to owners regarding the requirements for drug administration. Treatment dispensers and owners were instructed not to discuss the description of the trial drug or dosing regimen with the investigator. Due to the different dosing regimens of the two trial drugs, as well as the label requirement for the Atopica® capsules to be kept in their foil blister packaging until required for use, dog owners were not blinded in this study.

Drug administration

Oclacitinib was administered at a dose rate of 0.4–0.6 mg/kg p.o. twice daily for 14 ± 2 days, then once daily up to day 84 ± 2, with or without food. Ciclosporin was administered at a dose rate of 3.2–6.6 mg/kg p.o. once daily for the duration of the study. Owners of dogs in the ciclosporin group were instructed not to administer the trial drug within 2 h before or after feeding, according to the label directions. Day 0 of the study was defined as the first day of treatment for each enrolled dog.

Study schedule and variables measured

Baseline data (signalment, clinical history, concurrent medications, body weight, physical examination and assessments of pruritus and atopic dermatitis) were recorded for each dog enrolled in the study. Pruritus (assessed by the owner) and dermatitis (assessed by the veterinarian) were subsequently assessed at scheduled clinic visits on days 14 ± 2, 28 ± 2, 56 ± 2 and 84 ± 2; pruritus was also assessed by the owner at home on days 1, 2 and 7 ± 1. Pruritus was scored using an enhanced visual analog scale (VAS) consisting of a 10 cm line with text descriptors of severity and behaviour placed at 2 cm intervals.[17] The extent and severity of skin lesions were scored using the CADESI-02. On the final study day, the overall response to treatment (RTT) was assessed by both the owner and the veterinary investigator (not necessarily independently of each other) using a 10 cm VAS line, with a descriptor of 'no improvement' at 0 cm and 'excellent results' at 10 cm.

Owners and/or veterinarians were free to withdraw their dog from the study at any time due to an adverse event, worsening of clinical signs of AD or for any other reason; the reason for early withdrawal (or late completion) was recorded. Blood samples for haematology and serum chemistry were collected at enrolment (baseline) and on days 14, 28, 56 and 84; urine samples for general urinalysis were also collected at enrolment and on days 28 and 84. There was no specific requirement regarding the method of urine collection. Blood and urine samples were sent to a central veterinary diagnostic laboratory (Gribbles Veterinary Pathology, Clayton, Victoria, Australia). At scheduled and unscheduled clinic visits, a physical examination was performed and the dog's body weight recorded. Any abnormal clinical signs reported by the owner or identified by the examining veterinarian, as well as concurrent treatments, were recorded. Abnormal clinical signs were classified by the veterinary investigator at the time of observation as mild, moderate or severe, based on their clinical judgement.

Efficacy outcome measures

The primary efficacy measures assessed in this study were the percentage reduction from baseline score at each time point for both pruritus VAS and CADESI-02. Secondary efficacy variables included the following: (i) the absolute score at each time point for pruritus VAS and CADESI-02; (ii) the achievement of a ≥50% reduction from baseline score at each time point for pruritus VAS and CADESI-02; and (iii) owner and investigator RTT VAS on the final study day.

Some animals were excluded from the efficacy data set at specific time points due to dosing noncompliance, incorrect dose dispensed, administration of prohibited drugs, or if an efficacy assessment was performed outside the prescribed assessment window. Dogs with one or more major protocol deviations that affected the collection or integrity of their efficacy data were also excluded from the analysis.

Safety outcome measures

All dogs that received at least one dose of oclacitinib or ciclosporin were included in the safety summaries. For each continuous haematology, serum chemistry and urinalysis measure, summary statistics (mean, median, standard deviation, minimum and maximum) were calculated by treatment and time point. Haematology and serum chemistry values were summarized, reporting the number of dogs that fell below, within or above the normal reference range, as well as the number and percentage of dogs that had an increased shift (from below or within the reference range at baseline to above the reference range) or a decreased shift (from above or within the reference range at baseline to below the reference range) at each time point.

Frequencies of dogs reported to experience at least one abnormal health event were calculated by preferred adverse event term, based on the Veterinary Dictionary for Drug Related Affairs (VeDDRA) standard term list.[18] Descriptive statistics (mean, median, standard deviation, minimum and maximum) for body weight and percentage change from baseline body weight were calculated by treatment and time point. Frequencies of dogs receiving each concurrent medication recorded during the study were calculated.

Data analysis

Efficacy data were analysed using SAS version 9.2. Noninferiority tests of the percentage reduction from baseline of pruritus VAS scores and CADESI-02 scores on day 28 were performed at the one-sided 0.05 significance level with a delta of 15%; all other hypothesis tests were performed at the two-sided 0.05 significance level. For the percentage reduction and binomial analyses, the last time point data available were used as the day 28 values for dogs that were withdrawn from the study before day 28 due to worsening signs of atopic dermatitis or for an adverse event possibly related to the study drug.

The percentage reduction from baseline, for both pruritus VAS and CADESI-02, was analysed using a general linear mixed model for repeated measures, with the centred baseline value as a covariate. The fixed effects in the model were the covariate, treatment, time and treatment-by-time interaction. The random effects in the model were clinic, block within clinic, clinic-by-treatment interaction, treatment-by-block within clinic interaction (animal term) and residual.

Pruritus VAS scores and CADESI-02 scores were analysed using a general linear mixed model for repeated measures. The achievement of a ≥50% reduction from baseline score at each time point, for both pruritus VAS and CADESI-02, was analysed using a generalized linear mixed model for repeated measures with a logit link and binomial distribution, with the least-squares means being estimated proportions. The models were the same as for the percentage reduction variables without the covariate. Least-squares means investigator- and owner-assessed RTT VAS scores were analysed with a general linear mixed model. The fixed effect in the model was treatment and the random effects were clinic, block within clinic and residual.

An intention-to-treat analysis for the primary efficacy measures is available as Supporting Information (Tables S1 and S2).

Results

Baseline characteristics of the study population

A total of 226 dogs were enrolled in the study and received at least one dose of drug (Table 1). The most frequently represented breeds, either as a purebred dog or the predominant breed in a cross-bred dog, were as follows: Labrador retriever (12.4%), Staffordshire bull terrier (7.5%), Maltese (7.5%), beagle (5.3%), West Highland white terrier (4.9%) and miniature poodle (4.4%). Fewer than 15% of animals in each group were sexually intact.

Table 1. Baseline characteristics of the study population

Variable	Ciclosporin group	Oclacitinib group	*P*-Value
Purebred status [*n* (%)]			
Yes	64 (57.1)	74 (64.9)	—
No	48 (42.9)	40 (35.1)	—
Sex distribution [*n* (%)]			
Male	65 (58.0)	48 (42.1)	—
Female	47 (42.0)	66 (57.9)	—
Mean [range] age (years)	5.5 [1.0–13.5]	6.0 [1.0–14.0]	—
Mean [range] weight (kg)	19.5 [3.8–61.0]	20.6 [4.2–55.8]	—
Mean [range] pruritus VAS (cm)	7.4 [4.9–9.9]	7.4 [4.7–9.9]	0.7933
Mean [range] CADESI-02 score	57.3 [25–194]	61.9 [25–206]	0.3180

Study completion

A total of 176 of 226 (77.9%) animals completed the study as scheduled on day 84 ± 2; 19 animals in each group were withdrawn early (prior to day 82); five in each group completed the study late (after day 86); and two animals, both in the oclacitinib group, did not present for the final clinic visit. Table 2 summarizes the number of animals completing the study by period, as well as the reasons for early withdrawal or late completion.

Assessment of efficacy

The data set for the assessment of efficacy included >80 animals per treatment group at each time point for all variables measured and >100 animals per group for both primary outcome measures at day 28.

Owner-assessed pruritus VAS score

Oclacitinib had a significantly higher mean percentage reduction compared with ciclosporin on days 1, 2, 7, 14 and 28 (Table 3). Mean pruritus VAS scores at each time point are shown in Figure 1. There was a rapid reduction in mean pruritus score in the oclacitinib group from day 1 (5.6 cm) to day 14 (2.8 cm) and then a slight increase to 3.7 cm at day 28. On day 84, the mean score was below 3 cm for each treatment.

The estimated proportion of animals achieving a ≥50% reduction from baseline pruritus score at each time point is shown in Table 3; the proportion was significantly higher in the oclacitinib group at all time points up to day 28.

Investigator-assessed CADESI-02 score

Oclacitinib was significantly better than ciclosporin on day 14, with a mean reduction of 58.7% for oclacitinib compared with 43.0% for ciclosporin ($P < 0.0001$). On days 28, 56 and 84, the mean percentage reductions were similar in both treatment groups (Table 4); oclacitinib passed the statistical test of noninferiority for this variable on day 28. Mean CADESI-02 scores at each time point are shown in Figure 2; the scores decreased in both groups by day 14, with mean scores of 24.5 in the oclacitinib group and 31.2 in the ciclosporin group (not

Table 2. Study completion

Treatment group	Completed on schedule*[*n* (%)]	Withdrawn from study early or completed study late [*n* (%)]					Total (*n*)
		Day 1–12	Day 13–27	Day 28–55	Day 56–81	After day 86	
Ciclosporin	88 (78.6)	8 (7.1)	3 (2.7)	3 (2.7)	5 (4.5)	5 (4.5)	112
Oclacitinib	88 (77.2)	1 (0.9)	4 (3.5)	2 (1.8)	12 (10.5)	7 (6.1)§	114

	Reason for early withdrawal or late completion [*n* (%)]						
	Possible adverse reaction	Worsening signs of AD	Unrelated condition	Abnormal clinical pathology	Owner noncompliance¶	Other¶	
Ciclosporin	9 (37.5)†	3 (12.5)	0 (0)	1 (4.2)	4 (16.7)	7 (29.2)	24
Oclacitinib	3 (11.5)‡	6 (23.1)	3 (11.5)	1 (3.8)	5 (19.2)	8 (30.8)	26

*Final study visit on day 84 ± 2.

†Vomiting with or without diarrhoea in six dogs; urticarial vasculitis, neurological signs and flare in itch, each in one dog.

‡Vomiting, long-bodied *Demodex* and abdominal haematoma, each in one dog.

§Two dogs in the oclacitinib group did not present for the final study visit.

¶'Owner noncompliance' includes four dogs that completed the study late; 'other' includes six dogs that completed the study late and two that did not present for the final study visit.

significant, $P = 0.0763$). On day 84, the mean CADESI-02 score was below 20 for both treatments.

On day 14, there was a significantly higher proportion of animals in the oclacitinib group achieving a ≥50% reduction from baseline CADESI-02 compared with the ciclosporin group; proportions were similar in both treatment groups at subsequent time points (Table 4).

Overall response to treatment

The owner- and investigator-assessed RTT VAS scores were similar in both groups at the end of the study. For owner-assessed RTT, the mean scores were 7.1 cm for ciclosporin and 7.4 cm for oclacitinib ($P = 0.5053$); for investigator-assessed RTT, the mean scores were 7.3 cm for ciclosporin and 7.7 cm for oclacitinib ($P = 0.3494$).

Assessment of safety

Abnormal health events

The frequency of abnormal clinical signs occurring in two or more dogs in either treatment group, calculated on a per animal basis and excluding pre-existing conditions, is presented in the Supporting Information (Table S3).

Six animals in the ciclosporin group were withdrawn from the study due to vomiting (with or without diarrhoea), with four of these before day 7, and one animal from the oclacitinib group. New raised or nodular skin lesions (including lesions variously recorded as lump, mass, nodule, swelling, plaque, histiocytoma, papilloma or tumour) were found in 12 dogs (10.7%) in the ciclosporin group and in 12 dogs (10.5%) in the oclacitinib group; these skin lesions were biopsied in three ciclosporin-treated dogs and four oclacitinib-treated dogs. In the ciclosporin group, histopathological findings included the following: a melanocytic naevus (typically benign); changes consistent with but not clearly diagnostic of papilloma viral infection or an excessive lichenoid reaction to bacterial pyoderma; a sebaceous gland adenoma (benign); and a grade 1 mast cell tumour. In the oclacitinib group, histopathological findings were as follows: histiocytoma; follicular dilatation/orthokeratosis; suspect histiocytoma and nonspecific inflammatory changes; and chronic hyperplastic and ulcerative pododermatitis with fibroadnexal dysplasia.

Adverse events were classified by the veterinary investigator as severe in 17 animals (15.2%) in the ciclosporin group and 14 animals (12.3%) in the oclacitinib group. The majority of severe adverse events in both treatment groups were due to pre-existing conditions and/or concurrent disease, and many of these were due to potential complications of atopic dermatitis, such as bacterial pyoderma, fungal (yeast) skin infection and/or otitis externa. Severe adverse events not related to a pre-existing condition or concurrent disease occurred in six dogs in each treatment group. In the ciclosporin group, two animals developed severe vomiting following the first one or two doses and were withdrawn from the study; one animal had a severe flare in itch and was very distressed after two doses, and was withdrawn from the study; one animal developed numerous grey plaques on the trunk and limbs as well as an alopecic mass on a hindlimb; one animal developed severe diarrhoea on day 24, which resolved by day 28; and one animal developed severe anorexia and lethargy on day 47, which resolved by day 54. In the oclacitinib group, one animal experienced a chemical burn to the cornea on day 22; a mammary nodule was identified in one animal on day 60, which was subsequently biopsied and found to be a lipoma or normal mammary tissue; one animal developed elevated liver enzymes (alkaline phosphatase and alanine aminotransferase) on day 14, which increased further on day 21, so the animal was removed on day 25 for treatment of suspected bacterial cholangiohepatitis; and one animal had a firm swelling on the toe identified on day 56, which did not respond to antibiotics and continued to enlarge, so a biopsy was taken with a finding of chronic hyperplastic and ulcerative pododermatitis with fibroadnexal dysplasia. Two animals in the oclacitinib group were diagnosed with long-bodied *Demodex* (*Demodex injai*) infestation in skin scrapings taken from the dorsal trunk, one on day 28 and one on day 56. Both dogs were male West Highland white terriers, aged 4 and 7 years, with presenting clinical signs including dorsal erythema, scaly skin and/or a greasy hair coat. At the time of enrolment, each of these

Table 3. Least-squares mean percentage reduction from baseline and estimated proportion of animals achieving ≥50% reduction from baseline (95% confidence intervals) for owner-assessed pruritus VAS score at each post-treatment time point

Variable	Treatment group	Day of study						
		Day 1	Day 2	Day 7	Day 14	Day 28	Day 56	Day 84
Cases per group (*n*)	Ciclosporin	104	88	103	92	101	85	87
	Oclacitinib	110	100	107	109	103	92	83
Percentage reduction from baseline (%)	Ciclosporin	6.5 (2.3–10.7)	8.6 (4.5–12.7)	21.7 (16.6–26.8)	27.9 (22.0–33.8)	39.2 (33.2–45.2)	53.6 (46.7–60.4)	61.5 (54.4–68.6)
	Oclacitinib	25.6 (19.8–31.4)	41.4 (34.8–47.9)	56.6 (50.1–63.2)	63.2 (56.7–69.6)	50.9 (44.1–57.8)	53.5 (46.4–60.6)	61.0 (54.1–67.8)
	P-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0057*	0.9813	0.9047
Proportion ≥50% reduction from baseline	Ciclosporin	0.02 (−0.01 to 0.05)	0.01 (−0.02 to 0.04)	0.10 (0.04–0.17)	0.24 (0.15–0.32)	0.37 (0.27–0.46)	0.60 (0.50–0.70)	0.71 (0.61–0.81)
	Oclacitinib	0.19 (0.11–0.27)	0.41 (0.31–0.51)	0.58 (0.48–0.67)	0.68 (0.58–0.77)	0.51 (0.41–0.61)	0.63 (0.53–0.73)	0.66 (0.55–0.77)
	P-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0401*	0.7107	0.4779

*Significant treatment difference at $P < 0.05$.

cases had severe erythema on the dorsal thorax (i.e. a CADESI-02 score of 3), though skin scrapings were not performed on day 0. Based on CADESI-02 scores, none of the remaining nine West Highland white terriers had severe erythema on the dorsal thorax at the time of enrolment in the study.

One dog in the oclacitinib group developed an unrelated medical condition on day 1 and was euthanized at the owner's general veterinary clinic. This animal developed severe central nervous depression (obtunded mentation) and hyperglycaemic ketosis, believed to be caused by a poisoning because another dog in the same household developed similar clinical signs and had been euthanized 2 weeks previously. The animal's blood glucose level on day 0 was 16.3 mmol/L (reference range 3.3–6.7 mmol/L), indicating that this adverse event was likely to be due to a pre-existing condition.

Only minor changes in body weight were observed. By day 84, ciclosporin-treated dogs had gained on average 1.2% (range −14.3 to 15.8%) and oclacitinib-treated dogs had gained on average 3.4% (range −17.7 to 19.3%) compared with baseline body weight.

Haematology, serum chemistry and urinalysis

In both treatment groups, there were mild decreases in mean white blood cell, neutrophil, eosinophil and monocyte counts to day 28, which remained stable until day 84. While the mean counts remained within the normal reference range, individual animals in both treatment groups developed a leucopenia, primarily due to neutropenia, during the study. On day 84, slightly more animals in the oclacitinib group (14.4%) had a decreased shift in white cell count compared with the ciclosporin group (10.3%). The lowest individual white cell count recorded in each group was 3.6×10^9/L (reference range 6–17 $\times 10^9$/L). In both treatment groups, the mean lymphocyte count increased within the reference range to day 14, and then returned to baseline from day 28 until day 84. There was a trend of increasing mean haematocrit, haemoglobin and red blood cell count in both treatment groups over the course of the study, which was more pronounced in the ciclosporin group.

Only minor changes were observed in serum chemistry values over the course of the study, with group means and the number of animals outside the reference range remaining relatively stable in both treatment groups. A moderate proportion of enrolled dogs had one or more elevated liver enzymes at baseline; 15.9% in the ciclosporin group and 21.8% in the oclacitinib group for alkaline phosphatase and 9.1% in the ciclosporin group and 8.0% in the oclacitinib group for alanine aminotransferase. Mean liver enzyme levels remained stable in both treatment groups throughout the study.

Concurrent medications

The most commonly used (in ≥5% of dogs in either treatment group) concurrent medications are listed in the Supporting Information (Table S4) by drug class. Slightly more animals in the oclacitinib group received other dermatological preparations (largely medicated and nonmedicated shampoos) and topical antiseptics, whereas slightly more animals in the ciclosporin group

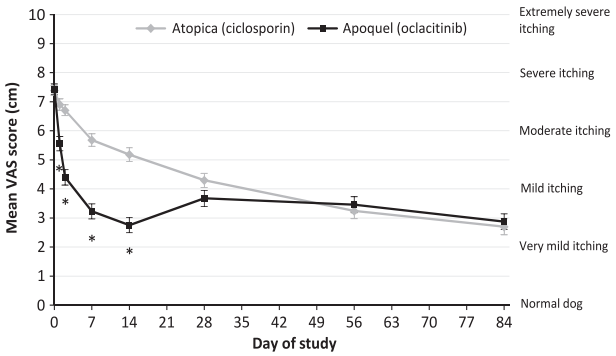

Figure 1. Least-squares mean owner-assessed pruritus visual analog scale (VAS) score at each time point; error bars indicate 1 SEM. *Significant treatment difference at $P < 0.05$.

received antibacterials for systemic and dermatological use, as well as otologicals.

Discussion

The results of this study indicated that the efficacy of oclacitinib for the control of canine AD is at least as good as that of oral ciclosporin and has a significantly faster onset of effect. The reduction in pruritus and skin lesions seen in the oclacitinib-treated dogs closely mirrored the results of a placebo-controlled study conducted in client-owned dogs in the USA,[15] suggesting consistently high efficacy of oclacitinib in populations of dogs with AD in different regions of the world. The percentage reduction from baseline pruritus VAS score and the proportion of dogs achieving ≥50% reduction from baseline were significantly better in the oclacitinib group in comparison to the ciclosporin group on days 1, 2, 7, 14 and 28 following initiation of treatment. After day 28, the level of pruritus continued to improve in both groups. Although there were no scheduled owner assessments between days 28 and 56, it was not until 8 weeks of treatment were completed that a similar improvement in pruritus was achieved in the ciclosporin-treated dogs compared with the oclacitinib-treated dogs. A limitation of this study was that owners were not blinded to treatment group allocation, due to the different dosing regimens of the two trial drugs as well as the label requirement for Atopica® capsules to be left in the blister packaging until required for use. This might have resulted in a degree of observation bias in assessments of pruritus, although the direction and extent of any bias would be difficult to quantify.

Improvement in skin lesions, as measured by the percentage reduction from baseline CADESI-02 score and the proportion of dogs achieving ≥50% reduction from baseline, was significantly better in the oclacitinib group on day 14. Oclacitinib passed the test of noninferiority on day 28, indicating that the efficacy of oclacitinib is at least as good as that of ciclosporin in terms of the percentage reduction from baseline CADESI-02 at that time point. By day 84, mean pruritus VAS scores in both groups were below 3 cm, corresponding to mild to very mild itching, and mean CADESI-02 scores were below 20. Only a small number of dogs were withdrawn early from this study due to worsening signs of AD; six in the oclacitinib group and three in the ciclosporin group. The dosage frequency of ciclosporin was not tapered in dogs that responded to treatment, largely due to the need to maintain blinding and the corresponding complexity of making decisions around clinical improvement and possible dose adjustment.

The antipruritic effect of oclacitinib was rapid, with mean reductions in pruritus of 25.6% on day 1, 41.4% on day 2 and 63.2% on day 14. In contrast, the control of pruritus in the ciclosporin group was slower, with mean reductions of 6.5, 8.6 and 27.9% on the same study days. Most dog owners are likely to be satisfied with the prescribed treatment for AD once their dog experiences a ≥50% improvement in the level of pruritus compared with baseline,[19] and this threshold has been used as a standard of efficacy in subsequent studies.[5] In the present study, there was a rapid increase in the number of oclacitinib-treated dogs achieving ≥50% reduction in pruritus score, with 19% of dogs on day 1 and 68% on day 14 reaching this threshold, compared with 2 and 24% of dogs, respectively, in the ciclosporin group. By day 84, pruritus scores in the oclacitinib group had returned to levels similar to those seen at the end of the twice-daily dosing period, indicating that once-daily therapy with oclacitinib is suitable for maintenance once the acute itch has been brought under control.

The rapid onset of effect of oclacitinib was consistent with that seen for prednisolone in a positive-controlled randomized clinical trial in client-owned dogs with allergic dermatitis.[20] In that study, both oclacitinib and prednisolone administered orally reduced pruritus levels substan-

Table 4. Least-squares mean percentage reduction from baseline and estimated proportion of animals achieving ≥50% reduction from baseline (95% confidence intervals) for investigator-assessed CADESI-02 at each post-treatment time point

		Day of study			
Variable	Treatment group	Day 14	Day 28	Day 56	Day 84
Cases per group (*n*)	Ciclosporin	93	101	85	87
	Oclacitinib	109	102	92	83
Percentage reduction from baseline (%)	Ciclosporin	43.0 (36.5–49.5)	54.4 (47.7–61.1)	61.8 (54.9–68.8)	65.4 (58.3–72.5)
	Oclacitinib	58.7 (52.3–65.0)	58.3 (51.6–65.1)	63.8 (56.9–70.8)	66.9 (59.7–74.0)
	P-value	<0.0001*	0.2799	0.6011	0.7065
Proportion ≥50% reduction from baseline	Ciclosporin	0.42 (0.30–0.53)	0.69 (0.57–0.80)	0.76 (0.65–0.87)	0.78 (0.68–0.89)
	Oclacitinib	0.71 (0.60–0.82)	0.65 (0.54–0.77)	0.77 (0.66–0.88)	0.82 (0.72–0.93)
	P-value	<0.0001*	0.6122	0.8816	0.5002

*Significant treatment difference at $P < 0.05$.

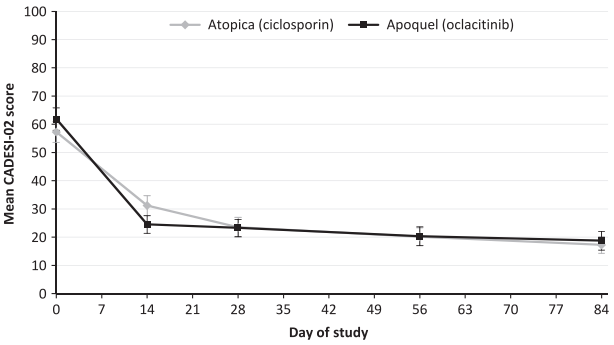

Figure 2. Least-squares mean investigator-assessed Canine Atopic Dermatitis Extent and Severity Index (CADESI)-02 score at each time point; error bars indicate 1 SEM.

tially within 4 ± 2 h, with mean percentage reductions in pruritus of the order of 30% at 4 ± 2 h, increasing to >40% by day 1. Bringing pruritus rapidly under control has been identified as a crucial factor in the overall management of allergic dermatitis,[21] in order to break the itch–scratch cycle and stop ongoing self-trauma to the skin, as well as providing the dog with some immediate relief.

Vomiting and/or diarrhoea were reported in over three times as many ciclosporin-treated dogs as oclacitinib-treated dogs, with the majority of these events occurring during the first 4 weeks of the study. In a 4 month study comparing ciclosporin and methylprednisolone for the treatment of canine AD, gastrointestinal signs were observed in 47 and 25% of dogs, respectively.[22] In the present study, six animals in the ciclosporin group were withdrawn due to vomiting, of which four cases occurred during the first week of treatment. In the oclacitinib group, one animal was withdrawn due to vomiting, as well as the development of a skin nodule, on day 14. Investigators commenced short-term antiemetic therapy in seven animals in the ciclosporin group; in all cases, maropitant citrate (Cerenia; Zoetis Australia Pty Ltd, West Ryde, NSW, Australia) was used.

Skin biopsies taken in a proportion of animals that developed a nodular skin lesion revealed most to consist of inflammatory, dysplastic or benign changes; a mast cell tumour (grade 1) was identified in one dog in the ciclosporin group. Skin lesions previously reported in dogs receiving ciclosporin therapy include cutaneous papillomatosis, hypertrichosis and lichenoid dermatosis,[5,23,24] while in dogs receiving oclacitinib, unspecified dermal lesions, histiocytomas and papillomas have been reported.[9,10,15] In a placebo-controlled study, one dog developed a grade 3 mast cell tumour after 60 days of oclacitinib treatment, while one placebo-treated dog developed a grade 1 mast cell tumour.[15]

In the present study, two dogs in the oclacitinib group were diagnosed with long-bodied *Demodex* (*D. injai*) infestation. Both animals were adult West Highland white terriers and had characteristic clinical signs of dorsal erythema, scaly skin and/or a greasy hair coat. Interestingly, both cases (but none of the other nine West Highland white terriers enrolled) had severe erythema of the dorsal thorax on day 0, so the possibility of *D. injai* being present in these two dogs at the time of enrolment cannot be ruled out. Previous reports of long-bodied *Demodex* infestation indicate that terriers are over-represented and that West Highland white terriers may be particularly susceptible.[25–27] It is plausible that concomitant disease, particularly atopic dermatitis, together with a subclinical sebaceous gland hyperplasia, may predispose dogs to infestation with *D. injai*.[27] Terrier breeds might therefore be more susceptible to this form of demodicosis because of their predisposition to develop AD.[27] It has been suggested that prior treatment with immunomodulatory or immunosuppressive drugs, such as prednisolone, dexamethasone, azathioprine or ciclosporin, could be a potential risk factor for *D. injai* infestation in terriers;[26] however, these drug therapies are also used for the treatment of AD, and a causal relationship has not been established.

Oclacitinib is a targeted treatment for the control of canine AD, with a rapid onset of action and a good safety profile. Based on the results of this study, oclacitinib has a faster onset of action and a lower frequency of gastrointestinal side effects than orally-administered ciclosporin.

Acknowledgements

The authors wish to thank the clinical investigators: Amanda Burrows, Greg Burton, Andrew Carter, Peter Hill, Beth McDonald, Michael Shipstone and Linda Vogelnest. We also thank the following Zoetis colleagues for their contributions: Candace Sousa, Mary Pat Gorman, Caroline Gadeyne and Nigel Edwards.

References

1. Griffin CE, DeBoer DJ. The ACVD task force on canine atopic dermatitis (XIV); clinical manifestations of canine atopic dermatitis. *Vet Immunol Immunopathol* 2001; 81: 255–269.
2. Marsella R, Sousa CA, Gonzales AJ *et al.* Current understanding of the pathophysiologic mechanisms of canine atopic dermatitis. *J Am Vet Med Assoc* 2012; 241: 194–207.
3. Olivry T, DeBoer DJ, Favrot C *et al.* Treatment of canine atopic dermatitis: 2010 clinical practice guidelines from the International Task Force on Canine Atopic Dermatitis. *Vet Dermatol* 2010; 21: 233–248.
4. Olivry T, Foster AP, Mueller RS *et al.* Interventions for atopic dermatitis in dogs: a systematic review of randomized controlled trials. *Vet Dermatol* 2010; 21: 4–22.
5. Olivry T, Bizikova P. A systematic review of randomized controlled trials for prevention or treatment of atopic dermatitis in dogs: 2008–2011 update. *Vet Dermatol* 2013; 24: 97–117, e25–e26.
6. Atopica Product Label (Australia). Novartis Animal Health Australasia Pty Ltd, North Ryde, NSW, Australia accessed 2011.
7. Steffan J, Favrot C, Mueller R. A systematic review and meta-analysis of the efficacy and safety of cyclosporine for the treatment of atopic dermatitis in dogs. *Vet Dermatol* 2006; 17: 3–16.
8. Burton G, Burrows A, Walker R *et al.* Efficacy of cyclosporin in the treatment of atopic dermatitis in dogs – combined results from two veterinary dermatology referral centres. *Aust Vet J* 2004; 82: 681–685.
9. Apoquel Product Label (United States). Zoetis Inc., Florham Park, NJ, USA. Available at: http://www.apoquel.com. Accessed Feb 14, 2014.

10. Apoquel Statement of Product Characteristics (European Union). Zoetis Belgium SA, Louvain-la-Neuve, Belgium. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/veterinary/002688/WC500152091.pdf. Accessed Feb 14, 2014.
11. Gonzales AJ, Humphrey WR, Messamore JE *et al.* Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013; 24: 48–53, e11–e12.
12. Gonzales AJ, Bowman JW, Fici GJ *et al.* Oclacitinib (APOQUEL®) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy. *J Vet Pharmacol Ther* 2014; 37: 317–324.
13. Fleck T, Humphrey W, Coscarelli E *et al.* Comparison of the Janus kinase (JAK) inhibitor, oclacitinib, and prednisolone in canine models of pruritus. *Vet Dermatol* 2012; 23(Suppl 1): 38 (abstract).
14. Cosgrove SB, Wren JA, Cleaver DM *et al.* Efficacy and safety of oclacitinib for the control of pruritus and associated skin lesions in dogs with canine allergic dermatitis. *Vet Dermatol* 2013; 24: 479–e114.
15. Cosgrove SB, Wren JA, Cleaver DM *et al.* A blinded, randomized, placebo-controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (Apoquel®) in client-owned dogs with atopic dermatitis. *Vet Dermatol* 2013; 24: 587–597, e141–e142.
16. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), Good Clinical Practice, June 2000, effective 1 July 2001. Brussels, Belgium.
17. Hill PB, Lau P, Rybnicek J. Development of an owner-assessed scale to measure the severity of pruritus in dogs. *Vet Dermatol* 2007; 18: 301–308.
18. European Medicines Agency. Guidance notes on the use of VeDDRA terminology for reporting suspected adverse reactions in animals and humans. EMA/CVMP/PhVWP/288284/2007-Rev.6, June 2013. London, UK.
19. Olivry T, Steffan J, Fisch RD *et al.* Randomized controlled trial of the efficacy of cyclosporine in the treatment of atopic dermatitis in dogs. *J Am Vet Med Assoc* 2002; 221: 370–377.
20. Little PR, Gadeyne C, King VL *et al.* Efficacy and safety of oclacitinib (Apoquel®) compared with prednisolone (Delta-Cortef®) for the control of pruritus and clinical signs associated with allergic dermatitis in client-owned dogs. *Vet Dermatol* 2014; 25: 156 (abstract).
21. Kircik LH. Efficacy and onset of action of hydrocortisone acetate 2.5% and pramoxine hydrochloride 1% lotion for the management of pruritus: results of a pilot study. *J Clin Aesthet Dermatol* 2011; 4: 48–50.
22. Steffan J, Alexander D, Brovedani F *et al.* Comparison of cyclosporine A with methylprednisolone for treatment of canine atopic dermatitis: a parallel, blinded, randomized controlled trial. *Vet Dermatol* 2003; 14: 11–22.
23. Robson DC, Burton GG. Cyclosporin: applications in small animal dermatology. *Vet Dermatol* 2003; 14: 1–9.
24. Favrot C, Olivry T, Werner AH *et al.* Evaluation of papillomaviruses associated with cyclosporine-induced hyperplastic verrucous lesions in dogs. *Am J Vet Res* 2005; 66: 1764–1769.
25. Hillier A, Desch CE. Large-bodied *Demodex* mite infestation in four dogs. *J Am Vet Med Assoc* 2002; 220: 623–627.
26. Robson DC, Burton GG, Bassett R *et al.* Eight cases of demodicosis caused by a long-bodied *Demodex* species (1997–2002). *Aust Vet Pract* 2003; 33: 64–74.
27. Ordeix L, Bardagí M, Scarampella F *et al. Demodex injai* infestation and dorsal greasy skin and hair in eight wirehaired fox terrier dogs. *Vet Dermatol* 2009; 20: 267–272.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Intention-to-treat analysis: Least-squares mean (95% confidence interval) percentage reduction from baseline for owner-assessed pruritus VAS score at each time point.

Table S2. Intention-to-treat analysis: Least-squares mean (95% confidence interval) percentage reduction from baseline for investigator-assessed CADESI-02 score at each time point.

Table S3. Abnormal clinical signs occurring in two or more dogs in either treatment group, excluding pre-existing conditions.

Table S4. Concurrent medications and therapies used in ≥5% of animals in either treatment group.

Résumé

Contexte – La ciclosporine est un traitement validé, sûr et efficace de la dermatite atopique (AD) chez le chien. Les études contrôlées contre placebo suggèrent que l'oclacitinib est une alternative thérapeutique sure et efficace.

Hypothèses/Objectifs – Evaluer l'efficacité et la sureté clinique de l'oclacitinib en comparaison avec la ciclosporine pour le contrôle de la dermatite atopique, par une étude clinique randomisée en aveugle, incluant un test de non infériorité à jour 28.

Sujets – Un total de 226 chiens de propriétaires ayant une anamnèse d'atopie, issus de huit sites, ont été inclus.

Méthodes – Les sujets enrôlés ont été randomisés pour recevoir de l'oclacitinib orale (0.4–0.6 mg/kg deux fois par jour pendant 14 jours, puis une fois par jour) ou la ciclosporine orale (3.2–6.6 mg/kg une fois par jour) pendant 12 semaines. Les propriétaires ont évalué le prurit à l'aide une échelle visuelle analogue (VAS) et les vétérinaires ont évalué les lésions par un CADESI-02 (Canine Atopic Dermatitis Extent and Severity Index).

Résultats – A jours 1, 2, 7, 14, 28, 56 et 84, le pourcentage de réduction du prurit évalué par les propriétaires évoluait de 25.6 à 61.0% dans le groupe oclacitinib comparé à 6.5 à 61.5% dans le groupe ciclosporine; les différences étaient significatives à tous les contrôles jusqu'au jour 28. Au jour 56, les chiens traités à la ciclosporine montraient une diminution du prurit identique aux chiens recevant de l'oclacitinib. A jour 14, le pourcentage de réduction du CADESI-02 était significativement meilleur dans le groupe oclacitinib (58.7%) que dans le groupe cilcosporine (43.0%). Trois fois plus d'effets indésirables gastro-intestinaux étaient rapportés dans le groupe ciclosporine comparé au groupe oclacitinib.

Conclusions et importance clinique – Dans cette étude, l'oclacitinib montre une meilleur rapidité d'action et une plus faible fréquence d'effets indésirables gastro-intestinaux que la ciclosporine dans le traitement de l'AD canine.

Resumen

Introducción – La ciclosporina es un fármaco aprobado para el tratamiento de la dermatitis atópica (AD) en perros y ha demostrado ser segura y efectiva. Los estudios controlados con placebo sugieren que oclacitinib es una terapia alternativa segura y efectiva.

Hipótesis/Objetivos – Evaluar la eficacia y seguridad de oclacitinib, en comparación con ciclosporina, al tratamiento y control de la dermatitis atópica en un ensayo clínico al azar, ciego e incorporando una prueba de no inferioridad en el día 28.

Animales – Se incorporaron al estudio un total de 226 perros de propietarios privados con historia de dermatitis atópica de ocho localizaciones distintas.

Métodos – Los animales incluidos un estudio se distribuyeron al azar para recibir oclacitinib (0,4 a 0,6 mg/kg dos veces al día durante 14 días, y después una vez al día) o ciclosporina oral (3,2–6,6 mg/kg una vez al día) durante 12 semanas. Los propietarios evaluaron el prurito utilizando una escala visual análoga reforzada (VAS), y los veterinarios valoraron la dermatitis utilizando el índice de extensión y severidad de la dermatitis atópica canina (CADESI)-02

Resultados – En los días 1,2, 7,14, 28,56 y 84, el porcentaje de reducción del valor basal en el prurito evaluado por los propietarios cambio de un 25,6 a un 61% para el grupo tratado con oclacinitib, comparado con un 6,5 a un 61,5% para el grupo tratado con ciclosporina; las diferencias fueron significativas en todos los tiempos hasta el día 28. En el día 56, los perros tratados con ciclosporina mostraron una disminución similar en el prurito a los perros tratados con oclacinitib. En el día 14, el porcentaje de reducción del valor basal en el CADESI-02 fue significativamente mayor en el grupo tratado con oclacinitib (58,7%) que en el grupo tratado con ciclosporina (43%). Se observan tres veces más efectos adversos gastrointestinales en el grupo tratado con ciclosporina.

Conclusiones e importancia clínica – En este estudio del tratamiento de la dermatitis atópica, el oclacinitib demostró una acción más rápida y con menor número de efectos gastrointestinales adversos comparado con la ciclosporina.

Zusammenfassung

Hintergrund – Ciclosporin ist für die Behandlung der atopischen Dermatitis (AD) der Hunde zugelassen und es hat sich als sicher und effektiv erwiesen.

Hypothese/Ziele – Eine Evaluierung der Wirksamkeit und Sicherheit von Oclacitinib im Vergleich zu Ciclosporin zur Kontrolle von AD in einer geblindeten, randomisierten klinischen Studie, bei der auch ein Nichtunterlegenheitstest am Tag 28 vorkam.

Tiere – Es wurden 226 private Hunde mit einer Anamnese von AD an acht Körperstellen in die Studie aufgenommen.

Methoden – Die Tiere wurden zufällig zur Verabreichung von Oclacitinib (0,4-0,6 mg/kg zweimal täglich für 14 Tage, dann einmal täglich) oder von Ciclosporin (3,2-6,6 mg/kg einmal täglich) für einen Zeitraum von 12 Wochen eingeteilt. Die BesitzerInnen beurteilten den Juckreiz mittels analoger Visualskala (VAS) und die TierärztInnen erfassten die Dermatitis mittels Canine Atopic Dermatitis Extent und Severity Index (CADESI)-02.

Ergebnisse – An den Tagen 1, 2, 7, 14, 28, 56 und 84 reduzierte sich der durch die BesitzerInnen beurteilte Juckreiz um 25,6 bis 61% vom Ausgangswert in der Oclacitinib Gruppe im Vergleich zu 6,5 bis 61,5% in der Ciclosporingruppe; die Unterschiede waren zu allen Zeitpunkten bis zum Tag 28 signifikant verschieden. Am Tag 56 zeigten die mit Ciclosporin behandelten Hunde eine ähnliche Juckreiz Verminderung wie die mit Oclacitinib behandelten Hunde. Am Tag 14 war die prozentuelle Verminderung vom Ausgangswert des CADESI-02 signifikant höher in der Oclacitinib Gruppe (58,7%) als in der Ciclosporingruppe (43,0%). Dreimal so viele Nebenwirkungen in Form von gastrointestinalen Symptomen wurden in der Ciclosporingruppe im Vergleich zur Oclacitinibgruppe beschrieben.

Schlussfolgerungen und klinische Bedeutung – In dieser Studie über die Behandlung der AD des Hundes zeigte Oclacitinib im Vergleich zu Ciclosporin einen rascheren Wirkungseintritt und eine niedrigere Frequenz von gastrointestinalen Nebenwirkungen.

要約

背景 – シクロスポリンはイヌにおけるアトピー性皮膚炎(AD)の治療に認可されており、安全かつ効果的であると証明されている。プラセボ−比較試験により、オクラシチニブが安全で効果的な代替療法であることが示唆されている。

仮説/目的 – 28日目で盲検的、ランダム化臨床試験で非劣性検定を併用して、ADのコントロールのためのオクラシチニブの効果および安全性を用いてシクロスポリンと比較し、評価すること。

供与動物 – 8ケ所の場所からのアトピー性皮膚炎の病歴のある合計226頭の飼い犬が組み入れられた。

方法 – 組み入れられた動物を経口オクラシチニブ(1日2回0.4-0.6 mg/kgで14日間、その後1日1回)、あるいは経口シクロスポリン(3.2−6.6 mg/kg1日1回)にランダムに割りあて、12週間与えた。飼い主は改良

されたビジュアルアナログスケール(VAS)でそう痒を評価し、獣医師はCanine Atopic Dermatitis Extent and Severity Index (CADESI)-02を用いて皮膚炎を評価した。
結果 – 1、2、7、14、28、56ならびに84日目に、飼い主が評価したそう痒のベースラインからの減少の割合は6.5%から61.5%に変化したシクロスポリン群と比較し、オクラシチニブ群では25.6%から61.0%に変化した。その差は28日までの全ての時点で有意であった。56日目において、シクロスポリンで治療されたイヌはオクラシチニブで治療したイヌと同等のそう痒の減少を示した。14日目において、CADESI-02のベースラインからの減少の割合は、シクロスポリン群(43.0%)に対して、オクラシチニブ群(58.7%)が有意に大きかった。オクラシチニブ群と比較し、シクロスポリン群では胃腸症状に起因する有害事象が3倍多く報告された。
結論および臨床的な重要性 – イヌADの治療におけるこの研究にて、オクラシチニブはシクロスポリンと比較し、効果が早く見られ、胃腸への副作用の頻度が少なかった。

摘要
背景 – 环孢素被批准用于犬异位性皮炎的治疗后,已经体现出有效性和安全性。双盲安慰剂对照研究认为oclacitinib是安全而有效的替代药物。
假设/目的 – 评估oclacitinib的安全性和有效性,对比环孢菌素,进行控制异位性皮炎的双盲随机临床试验,纳入28天非劣效性实验。
动物 – 动物主人的226只犬,均有异位性皮炎病史,分别来自8个机构提供的登记信息。
方法 – 登记动物随机给予口服oclacitinib(0.4–0.6 mg/kg 一日两次 ,连服14日,之后改为一日一次)或口服环孢素(3.2–6.6 mg/kg 一日一次),连续给药12周。主人用增强视觉模拟评分法(VAS)评估瘙痒,兽医用犬异位性皮炎程度与严重性指数(CADESI)-02评估皮炎。
结果 – 在第1、2、7、14、28、56和84日时,主人评估的瘙痒程度减少率,oclacitinib为25.6%至61.0%,环孢素组为6.5 %至 61.5%;28天内各时间点的差异显著。在第56日,环孢素和oclacitinib治疗患犬瘙痒减轻率相同。第14天时,oclacitinib组瘙痒减轻率(58.7%)明显大于环孢素组(43.0%)。环孢素组的胃肠不良反应是oclacitinib组的三倍。
总结与临床意义 – 在此次犬异位性皮炎的治疗研究中,与环孢菌素相比,oclacitinib的起效速度快,并且胃肠道反应少。

