Veterinary Dermatology

Vet Dermatol 2015; **26**: 432–e101 DOI: 10.1111/vde.12250

Efficacy of ultra-micronized palmitoylethanolamide in canine atopic dermatitis: an open-label multi-centre study

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Background – Palmitoylethanolamide is a naturally occurring bioactive lipid, produced on-demand by damage-exposed cells. Palmitoylethanolamide is documented to counteract inflammation, itch and pain.

Objective – The aim of this 8-week study was to evaluate the efficacy of oral ultra-micronized palmitoylethanolamide (PEA-um) in dogs with moderate atopic dermatitis.

Animals – Clinicians from 39 veterinary clinics enrolled 160 dogs with nonseasonal atopic dermatitis and moderate pruritus.

Methods – This was a multi-centre open-label study. On days 0 (D0) and 56 (D56), owners evaluated pruritus with a Visual Analog Scale (VAS) and completed a validated Quality of Life (QoL) questionnaire. Veterinarians assessed the severity of skin lesions using the Canine Atopic Dermatitis Lesion Index (CADLI).

Results – Mean pruritus VAS score decreased from 5.7 ± 0.08 cm (range 3.8–7.9 cm) to 3.63 ± 0.19 cm (range 0.1–9.2 cm) ($P < 0.0001$). At D56, 58% of dogs showed a greater than 2 cm reduction from baseline and 30% showed an absent-to-very mild pruritus (VAS ≤ 2 cm). Mean total CADLI at D56 decreased significantly ($P < 0.0001$); in 62% of dogs this score reached a value in the remission range (≤5). Mean total QoL score was significantly decreased ($P < 0.0001$) with 45% of dogs reaching QoL values described for healthy animals. Tolerability was good-to-excellent with only four dogs reporting treatment associated reversible adverse events.

Conclusions and clinical importance – PEA-um appears to be effective and safe in reducing pruritus and skin lesions, and in improving QoL in dogs with moderate atopic dermatitis and moderate pruritus.

Introduction

Canine atopic dermatitis (cAD) is a "genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE, most commonly directed against environmental allergens".[1] Canine AD affects up to 15% of the canine population worldwide and accounts for up to 27% of the animals referred for pruritus.[2] Persistent pruritus is an essential feature of cAD, such that its diagnosis requires a history of itching.[3] Cutaneous lesions such as erythema, excoriations and self-induced alopecia may reflect the severity of pruritus.[4] Reduced quality of life (QoL) – for both dogs and owners – is a critical net result and has by far the greatest impact on health, wellbeing and the human–animal bond.[5–7]

Current guidelines highlight the need for a multifaceted and integrated treatment approach for cAD.[8,9] These include avoidance of flare factors (e.g. allergens), skin and coat hygiene and care, and control of skin infections, as well as allergen-specific immunotherapy and pharmacotherapy to alleviate pruritus and skin lesions.[8–11]

Palmitoylethanolamide (PEA) is a naturally occurring bioactive lipid compound and an endocannabinoid-like

Accepted 6 June 2015
Sources of Funding: This work was supported by the Italian Ministry of Instruction, University and Research grants (MIUR; PON01-02512).
Conflict of interest: CN is a consultant for Innovet Italia Srl, also for Zoetis, Elanco and ICF. AM and CM are employees of Innovet Italia Srl. MFdV is a consultant for Innovet Italia Srl and a co-inventor in patents on the use of palmitoylethanolamide for the treatment of inflammation and pain.
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molecule.[12] Endocannabinoids and related mediators such as PEA are produced on-demand in response to stress and tissue damage, and play a key role in regulating cutaneous inflammation and immunity.[13,14] The possible mechanisms of action of PEA may include the downregulation of mast cell degranulation, including canine mast cells,[15] and through the process termed Autacoid Local Injury Antagonism.[12,16,17] PEA is present in a variety of food sources (e.g. egg yolk, soybean lecithin, bovine milk) as well as in almost all mammalian body fluids and tissues, including the skin, where it is synthesized, released and degraded.[18] PEA is found also in the skin of healthy and atopic dogs,[19] where endocannabinoid receptors (i.e. indirect molecular targets of PEA[12]) have been detected.[20] Skin levels of PEA are up to 30-fold higher in atopic dogs compared with healthy dogs;[19] previous studies point to the potential usefulness of PEA in managing allergic responses in companion animals[21–23] and experimental settings.[12,18,24,25] Such studies, although promising, have several design limitations, thereby highlighting the need for additional investigations.

Ultra-micronized PEA (PEA-um) is a patented, pharmaceutical grade formulation in which >99% by weight of PEA has particle sizes below 6 μm. Ultramicronization is frequently used to improve the bioavailability and efficacy of a very low water-solubility molecules through an increased dissolution rate of the micron-size substance.[26,27] The superiority of PEA-um over nonmicronized naïve PEA was demonstrated in an experimental model of inflammatory pain.[28] Furthermore, a study of beagle dogs with spontaneously occurring *Ascaris* hypersensitivity showed that a single oral dose of PEA-um (10 mg/kg once daily) significantly reduced the wheal area induced by intradermal injection of antigen and anti-canine IgE.[29]

We evaluated the efficacy and safety of oral PEA-um administration in client-owned dogs with symptomatic and stable nonseasonal cAD. Our objectives were to determine whether daily administration of PEA-um for a two month period could affect pruritus (primary outcome) and skin lesions and QoL (secondary outcomes) in dogs with cAD.

Materials and methods

Overview

This study was designed as an 8-week, open-label, multi-centre trial. Dogs were recruited from 39 veterinary clinics throughout Italy. Participating clinicians formed the "Skinalia Clinical Research Group". The study did not have to be assessed for ethical standards under the Italian Minister of Health's Decree of 12 November 2011 (clinical testing of veterinary drugs) because PEA is classified as a feed material (and not veterinary drug) according to Regulation (EC) No 767/2009. Owners gave informed written consent for their dogs to participate in the study and were free to withdraw at any time without prior notice.

Enrollment criteria

Client-owned dogs (irrespective of breed or sex) with visible signs of nonseasonal pruritic skin disease were included, based on published diagnostic criteria for cAD.[30] In particular, the first set of eight criteria was used and dogs had to fulfill at least five to be included. The criteria were as follows: (i) age at onset <3 years; (ii) mostly indoor; (iii) corticosteroid-responsive pruritus; (iv) chronic or recurrent yeast infections; (v) affected front feet; (vi) affected ear pinnae; (vii) nonaffected ear margins; and (viii) nonaffected dorso-lumbar area. Moreover, dogs with cAD had to fulfill the entry criteria listed in Table 1. Throughout the study period (56 days) dogs were kept in their usual environment with their owners, ate their usual diet, received routine antiparasitic prophylaxis and were taken to the clinician for regular visits.

Study protocol

Each clinician had to schedule and perform three visits [days 0 (D0), D28 and D56] and one telephone interview (D15) for each successfully enrolled patient.

A validated owner-assessed 10 cm Visual Analog Scale (VAS) with descriptors was used for evaluation of pruritus severity.[31] The distance (in cm) from the bottom of the line to the owner's mark was measured and recorded. Owners performed a pruritus assessment on D0, D28 and D56.

A validated lesion scale, called Canine Atopic Dermatitis Lesion Index (CADLI),[4] was used to assess cAD lesion severity on D0, D28 and D56. Briefly, CADLI considers only the body regions most frequently affected in atopic dogs (head and pinnae, forefeet, hind feet, ventral thorax and axillae, ventral abdomen and inguinal region) and scores two lesion type subclusters (i.e. "erythema-excoriation-erosion", hereinafter referred to as CADLI1 and "alopecia-lichenification-hyperpigmentation" hereinafter referred to as CADLI2) on a six-point ordinal scale (0–5; see Table 2).

A 15-item validated questionnaire on the QoL of dogs with skin disease and their owners was used.[6,7] The questionnaire is subdivided into three main sections: (i) disease severity (question 1); (ii) dog's QoL (QoL1, questions 2–8); (iii) owner's QoL (QoL2, questions 9–15). Owners were asked to complete the QoL questionnaire on D0, D28 and D56. In order to assess the speed of treatment response, a telephone interview was carried out on Day 15 by the clinician or by the study monitor. Owners were asked to state if itching of their dog was (i) the same, (ii) more severe, or (iii) less severe than on Day 0.

Table 1. Enrollment criteria.

Inclusion criteria

1. CADLI score, as assessed by the clinician, <23 (corresponding to mild-to-moderate cAD on an overall assessment basis)[4]
2. Pruritus VAS score,[31] as assessed by the owner, of ≥3.6 cm, <8 cm (corresponding, on a descriptive basis, to mild to severe itching; very mild and extremely severe pruritus being excluded)
3. Regularly receiving (the same) antiparasitic prophylaxis before entering and during the study
4. Maintaining the same diet and environment before entering and during the study
5. Overall good health, apart from cAD
6. Owner's statement to comply with the protocol and signed written informed consent

Exclusion criteria

1. Clinical evidence of bacterial or fungal infections
2. Any systemic or dermatologic causes of pruritus other than cAD
3. Improvement of pruritus and lesions with a hypoallergenic diet and subsequent deterioration upon challenge with the original food
4. Orally administered antihistamines or fatty acids and topically applied corticosteroids <2 weeks prior to enrollment
5. Orally administered corticosteroids <4 weeks prior to enrollment
6. Treatment with depot-corticosteroids or systemic immunomodulators (e.g. ciclosporin) <8 weeks prior to enrollment
7. Allergen-specific immunotherapy introduced <12 months before enrollment
8. Owner willing to start other additional treatments – both pharmacological and nutritional – including topical antipruritic agents (i.e. creams, sprays and shampoos) during the study period

cAD, canine Atopic Dermatitis; CADLI, Canine Atopic Dermatitis Lesion Index; VAS, Visual Analog Scale.

Table 2. Body regions and lesion type subclusters for the Canine Atopic Dermatitis Lesion Index (CADLI). Each body region was scored 0–5, integrating the severity and extent of the lesion(s) in the area (see reference 4 for a detailed description of the lesion index).

Body region	Score (per body region)	CADLI	
		CADLI1	CADLI2
1. Head and pinnae 2. Forefeet 3. Hind feet 4. Ventral thorax and axillae 5. Ventral abdomen and inguinal	0–5	Erythema Excoriation Erosion	Alopecia Lichenification Hyperpigmentation

On the final day of study both investigator and owner satisfaction were recorded for each enrolled dog, regardless of whether or not they had completed the study. The clinician was asked to rate the overall effectiveness of the treatment as being excellent, moderate, good, mild or absent. Owners were asked to rate how their dogs felt following treatment, the possible answers being: worse, a little better, much better, or "I cannot answer".

Assessment of efficacy

The primary outcome measure was the change in pruritus severity at 8 weeks from baseline. In particular, treatment was considered successful if the pruritus VAS showed a >2 cm reduction at the end of the study compared with the initial value at D0. Secondary outcome measures were changes in lesion severity and QoL at 8 weeks compared with values at D0. The secondary outcomes were: (i) the percentage of dogs with a lesion score reduction of ≥50%, (ii) the percentage of dogs that ended the study with a lesion score in the "normal" range (i.e. ≤5)[4] and (iii) the percentage of dogs finishing the study with QoL1 and QoL2 values within limits described for healthy dogs, corresponding to 2 and 5, respectively.[6,7]

Tolerability

Tolerability was assessed by monitoring and recording adverse events (AEs) and withdrawals at any time during the study. An AE was defined as: "any unfavourable diagnosis, sign or syndrome shown by the participant that either occurred during the study, having been absent at D0 or, if present at D0, appeared to worsen". An AE was reported even if its occurrence was not necessarily caused by or related to the product. All untoward effects that occurred during the study were recorded by clinicians on an AE reporting form, together with their onset, severity and perceived association with the study product. Clinicians were instructed to use their knowledge of the dog, the circumstances surrounding the event and an evaluation of any potential alternative causes to determine whether or not an AE was related to the study product. They indicated "yes" or "no" accordingly. This determination was recorded in the case report form and was not questioned by the sponsor.

Study product

The study product contained PEA (also known as Palmidrol INN, International Nonproprietary Name) in ultra-micronized form (PEA-um) and was provided in soft gelatine capsules in two different strengths, 50 and 150 mg. The owner administered the product orally once daily, for the entire study period (56 days) on the basis of a daily dose of PEA-um equal to around 10 mg/kg body weight. Dogs weighing 0–6 kg received one 50 mg capsule; those weighing 7–12 kg received two 50 mg capsules; those weighing 13–19 kg one 150 mg; those weighing 20–35 kg received two 150 mg capsules; and those weighing >35 kg received three 150 mg capsules.

Concomitant treatment

During the study period any topical or systemic treatment different from the study product (e.g. corticosteroids, ciclosporin and antimicrobials) was not allowed, except for antiparasitic prophylaxis, allergen-specific immunotherapy (if started more than 12 months before inclusion with no significant results), shampoo therapy, ear cleansing and routine grooming, provided that they had not been changed by at least 2 months prior to enrollment.

Statistical procedures

Data were analysed using SAS v9.2 (SAS Institute, Cary, NC, USA). The level of significance was set at $P < 0.05$. All analyses were performed on those subjects that had at least one assessment after baseline and were not considered protocol violations. Data are expressed as mean ± standard error (SE), unless otherwise stated.

The response to treatment of the three efficacy outcome measures (pruritus-VAS, CADLI and QoL) on the three time points (D0, D28, D56) was analysed using a generalized linear mixed model (GLMM) for repeated measures. The fixed effects in the model were age in months, sex, reproductive status, weight and time. The random effect in the model was animal. The nonparametric Wilcoxon signed-rank test was also used as a *post hoc* analysis on the final effect (D56–D0). The GLMM and Wilcoxon test were also used to analyse the treatment response of the measured subclusters [i.e. CADLI1, CADLI2 and QoL (severity), QoL1, QoL2]. *P*-values were adjusted with the Holm–Bonferroni correction for multiple comparisons. The *post hoc* analysis on the effect by the severity class at enrollment for pruritus-VAS, CADLI and QoL was performed using the Kruskal–Wallis test. The Pearson correlation between the response of pruritus to treatment and that of CADLI and QoL was also performed.

Results

Demographics

A total of 160 dogs were enrolled between February and December 2013. Sixty six were males (41.3%) and 94 females (58.8%). Fifty seven females (61%) and 11 males (17%) were neutered. Mixed breed dogs were

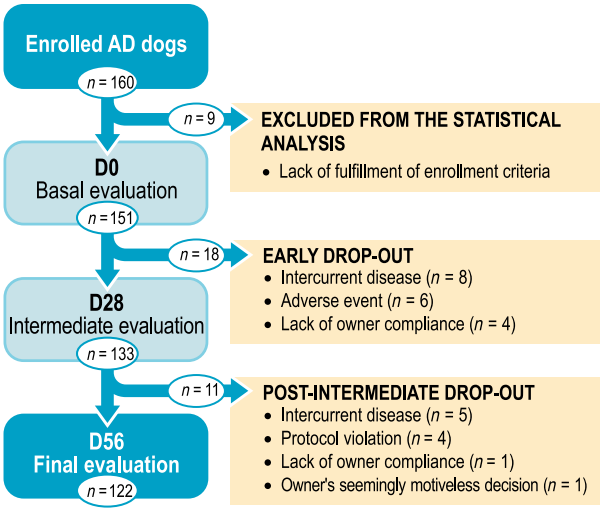

Figure 1. Study flow diagram. The term "intercurrent disease" refers to a disease that develops in and may alter the course of canine atopic dermatitis (e.g. Malassezia otitis, pyoderma), as well to an unanticipated disease (e.g. injury from dog bite or car accident). The term "adverse event" refers to the appearance of signs potentially unrelated to the disease course and/or worsening of the skin condition.

most commonly represented (n = 37; 23.1%), followed by the Labrador retriever (n = 12; 7.5%), West Highland white terrier (n = 10; 6.3%) and Jack Russell terrier (n = 9; 5.6%); all other breeds were represented by <5% of study subjects. Mean body weight was 18.1 kg (range 2.0–70.0; median 14.3). Mean age was 5 years (range 10 months–15 years). Nine dogs were excluded from the analysis because of initial failure to meet the enrollment criteria, 18 dogs dropped out early (before the intermediate visit at D28) and 11 dogs had a post-intermediate drop-out (between D28 and D56). The detailed flow diagram on the numbers and reasons for withdrawal is shown in Figure 1. One hundred and thirty-three dogs that had at least one assessment (in addition to baseline) and no protocol violations were included in the statistical evaluation.

Treatment dose

The individual daily dose for analysed dogs was 10.9 mg/kg (range 6.4–25.0, median 10.7).

Pruritus

The mean pruritus score at D0 was 5.7 ± 0.08 cm (corresponding to moderate itching), ranging from 3.8 to 7.9 cm. According to the pruritus VAS descriptors,[31] the study dogs suffered from mild to severe itching, with the following distribution: n = 5 (4%) with a mild pruritus score ≤4 cm; n = 91 (68%) with a mild-to-moderate score ranging from 4 cm to 6 cm; and n = 37 (28%) with a moderate-to-severe score >6 cm.

The proportions of dogs exhibiting a positive response to treatment (i.e. whose pruritus score at D28 and D56 decreased from baseline level) were 80% and 83%, respectively. A decline in the proportion of cases with a moderate-to-severe pruritus (from 96% at D0 to 39% at D56), matched a similar rise in the proportion of dogs with absent-to-mild pruritus (from 4% at D0 to 61% at D56). The mean pruritus score at D56 was 3.63 ± 0.19 (range 0.1 to 9.2 cm), resulting in a 36% reduction in pruritus during the study treatment period ($P < 0.0001$) (Figure 2a). According to the *post hoc* analysis of the effect of treatment by severity class, treatment decreased pruritus regardless of the initial pruritus score. Indeed, the mean decrease of pruritus scores at 8 weeks from D0 was not statistically different between severity classes, corresponding to 2.1, 2.2 and 2.2 for mild, moderate and severe pruritus, respectively (Figure 2b).

At study end (D56), 71 out of 122 dogs showed a greater than 2 cm reduction on VAS from baseline, translating to a 58% treatment success rate (Table 3). Although using 50% improvement as a primary outcome measure is not necessarily recommended,[31] the value was calculated for comparison purposes with previous studies: 35% of dogs showed a 50% or greater reduction in pruritus at the end of the study (Table 3). Moreover, 30% of dogs (n = 36) reached a VAS score of 2.0 cm or less by D56, thus exhibiting a "normal" level of pruritus, thus a level comparable to that of dogs without skin problems and regarded by many owners as not worthy of veterinary attention[31] (Table 3). Analysis of the D15 telephone interview showed that 7% of cases suffered more pruritus than baseline. Forty five percent of owners perceived their dog's pruritus to be unchanged and 48%

Table 3. Primary and secondary outcome measures

	D28		D56	
	N (133)	%	*N* (122)	%
Pruritus (VAS)				
VAS reduction ≥ 2.0 cm	**54**	**41**	**71**	**58**
VAS ≤ 2.0 cm ("normal")	28	21	36	30
VAS reduction ≥ 50%	31	23	43	35
Lesion severity (CADLI)				
CADLI ≤ 5	58	44	76	62
CADLI reduction ≥ 50%	49	37	78	64
Quality of life				
QoL1 ≤ 2	42	32	55	45
QoL2 ≤ 5	49	37	59	48

CADLI, Canine Atopic Dermatitis Lesion Index. VAS, Visual Analog Scale.
The number of dogs (*N*) and the relative percentage are reported for both the intermediate (Day 28, D28) and final visit (D56). Data in bold represent the treatment success rate for pruritus.

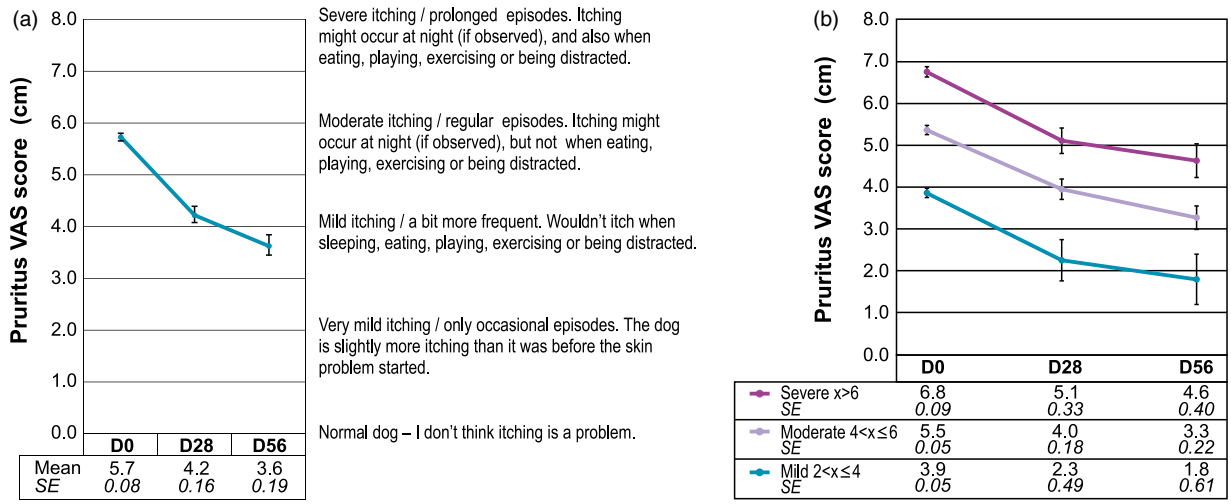

Figure 2. Effect of treatment on pruritus. (a) Mean reduction of pruritus severity as assessed by the owner. (b) Change of pruritus severity in response to treatment: comparing three sub-groups initially based on the severity at Day 0 (x, mean Visual Analog Scale score; SE, standard error).

answered that pruritus was less severe than at study entry.

Lesions

At D0 the mean severity of lesions, based on the CADLI total score,[4] was 11.4 ± 0.44 (range 2–22), corresponding on average to moderate cAD. Based on validated thresholds for CADLI to predict a dog's overall assessment,[4] 12 dogs (9%) were considered to be in remission phase (CADLI score < 5), 97 (73%) had mild cAD (CADLI score ranging from 5 to 7) and 24 (18%) had moderate cAD (CADLI score ranging from 7 to 23). In 80% of dogs the CADLI score at D28 and D56 decreased from D0. The decrease was ≥50% in 49 and 78 dogs at D28 and D56, respectively (Table 3). The percentage of moderately affected dogs gradually decreased (75% at D0 versus 24% at D56), in favour of dogs with a score compatible with disease remission (9% at D0 versus 62% at D56). Thus, 62% of dogs reached a final CADLI index ≤5, which is the benchmark for cAD in remission[4] (Table 3). The mean CADLI score at study end was 5.9 ± 0.54 (range 0–37). The decrease in mean total CADLI score was 46.5% ($P < 0.0001$) at study end (Figure 3a). When the two lesion subsets were considered separately (CADLI1: erythema/excoriations/erosions; and CADLI2: alopecia/lichenification/hyperpigmentation), the mean percentage decreases at D56 from baseline were 50% and 40% for CADLI1 and CADLI2, respectively. The response to treatment of the single CADLI subclusters was statistically significant ($P < 0.0001$) with CADLI1 showing a greater marginal reduction than CADLI2 ($P < 0.0001$) (Figure 3b). In contrast to pruritus, the response of skin lesions to treatment differed significantly depending on initial lesion severity ($P < 0.0001$). In particular, the higher the baseline severity index, the greater was the effect of treatment (Figure 3c).

Quality of life

At D0, study dogs had a mean global QoL questionnaire score of 17.0 ± 0.62, with a mean severity score (question 1) of 1.6 ± 0.07 and mean QoL1 and QoL2 scores of 6.3 ± 0.31 and 9.0 ± 0.34, respectively. Percentages of dogs whose QoL value improved in response to treatment were 70% and 76% at D28 and D56, respectively. At study end, 45% and 48% of dogs recorded, respectively, QoL1 and QoL2 scores corresponding to a healthy dog (≤2 and ≤5)[6,7] (Table 3).

The mean improvement over baseline was >30% both for total QoL and its subsets (severity, QoL1 and QoL2) and was statistically significant in all instances ($P < 0.0001$). In particular, the mean improvement for total QoL was 33% (17.0 ± 0.62 at D0 versus 11.4 ± 0.74 at D56); 36.1% and 30.4%, respectively, for QoL1 (dog) and QoL2 (owner) and 34.8% for QoL (severity).

Relationship between primary and secondary outcomes

A positive linear relationship was found between the treatment effects on pruritus and skin lesions ($r = 0.64$; $P < 0.0001$). Similarly, a positive linear relationship was found between the treatment effects on pruritus and QoL ($r = 0.67$; $P < 0.0001$). These moderate to strong positive linear correlations (Pearson's coefficient > 0.6), indicate that the size effect on pruritus increased in step with the size effect on lesions and QoL.

Overall clinician and owner satisfaction

Out of 160 enrolled dogs, 146 "study end forms" were completed by the clinician. Nearly half ($n = 70$, 48%) rated the overall treatment effectiveness to be "good" or

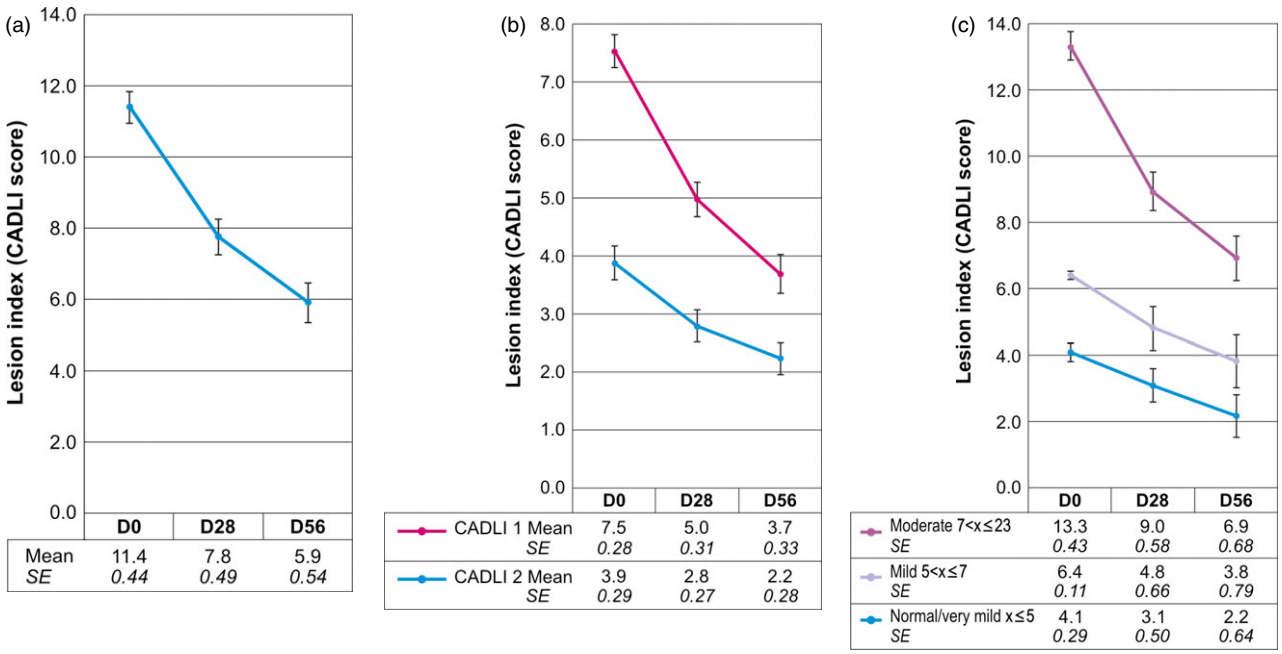

Figure 3. Mean reduction of lesion severity as assessed by the clinician. (a) total Canine Atopic Dermatitis Lesion Index CADLI. (b) CADLI subclusters. (c) Change of lesion severity in response to treatment, comparing three sub-groups based on the lesion severity index at Day 0 (x, mean CADLI global score; SE, standard error).

"excellent". Twenty seven percent (n = 40) graded clinician satisfaction as "sufficient" and 16% (n = 24) poor. There was 8% of "study end forms" (n = 12) where treatment was reported not to be effective from the clinician's point of view. One hundred and forty-four "study end forms" were filled by the owners. Nineteen (13%) reported the owner unable to rate dog wellbeing following treatment. Sixteen forms (11%) stated that the dog was worse, 59 (41%) a little better and 16 (35%) much better than before entering the study.

Assessment of safety

Eleven of 160 case report forms (7%) registered the occurrence of an AE. Six of these AEs led to discontinuation (adverse early drop-outs), whereas the remaining five did not. One hundred and forty-nine forms (93%) were submitted with "no adverse event". Seven of 11 AEs fell into the "abnormal health event" type, whereas the remaining four were due to "worsening skin condition" (Table 4). In four cases (2.5%) the AE was considered to be related to the study product and two of these cases were withdrawn from the study.

Discussion

In this study PEA-um significantly improved pruritus, skin lesions and QoL in dogs suffering from moderate cAD. Based upon previously reported cut-off points,[4,31] dogs showed a moderate degree of pruritus and lesion severity at enrollment. Regarding pruritus, the large majority of dogs experienced mild or mild-to-moderate itch (72%) and a further 28% moderate-to-severe itch. Such a distribution depends on the selected entry cut-offs (≥3.6 cm, <8 cm on the VAS scale), chosen to exclude dogs with very mild or extremely severe itch. Very mild cases were not included either because of the difficulty in detecting improvement of only a few points and because the dogs could improve on their own (relapsing–remitting course). Very severe cases were excluded for ethical reasons. A high cut-off point was chosen for lesions, meaning that severe cases (CADLI ≥ 23) were not included (for ethical reasons), whereas a low cut-off was not established; the primary endpoint of the study was the effect of PEA on pruritus. Based on our experience and these cut-off points, we believe the study sample to be representative of atopic dogs usually presented to veterinary clinicians in Italy.

The PEA-um effect on pruritus was the primary outcome in this study and was statistically significant. Nearly 80% of dogs improved in the first month. This is similar to previous findings for ciclosporin[32] and better than results reported with tepoxalin and misoprostol, the latter achieving reductions of pruritus in 46% and 64% of dogs, respectively.[33,34] In the present study we observed a 36% reduction in the mean pruritus score. Although the present study was an open design, the mean percentage reduction in pruritus was higher than that previously reported for the placebo in controlled studies, which ranged between 11% and 20%.[34–38] Among published reports, the percentage of dogs whose pruritus improved more than 50% at study end ranged from 11% to about 80%.[36,37,39–47] Our result of 35% lies in the middle, being lower than that of prednisolone[44] and higher than antihistamines.[46] PEA-um decreased pruritus to an extent comparable to that of treatments used for cAD (see Table S1 in Supporting information).[35–40,42–45,48–50] The success rate of the study was around 60% (i.e. 71 out of 122 dogs showed a >2 cm reduction of their pruritus score from baseline, this representing a shift to a lower severity class), similar to that reported by others.[36]

Of interest in our investigation is that 30% of dogs achieved a pruritus score of ≤2 cm at study end. Importantly, the number of dogs that ended up with a pruritus score in this range is considered to reflect the intervention's true efficacy in the field.[31] Because this score is essentially regarded as a "normal" level of pruritus (a level at which most owners would not seek veterinary attention),[31] it is reasonable to conclude that PEA-um decreased pruritus to normal levels in almost one third of atopic dogs. This result is similar, albeit slightly lower, to

Table 4. Adverse events (chronological order of appearance with respect to treatment duration), sub-grouped in two categories: abnormal health event (i.e. appearance of signs potentially unrelated to the disease course); worsening skin condition (e.g. increased pruritus); n, neutered.

Breed	Sex	AE description	Days of treatment before AE	AE related to study product?	Dog completed the study?
		Abnormal health event			
Standard bull terrier	M (n)	Polyuria during the first few days of treatment	1	Yes	Yes
Pug	F (n)	Vomiting, diarrhoea, severe facial itch	4	No	No
West Highland white terrier	F (n)	Borborygmi and occasional vomiting and loose stools	7	No	Yes
Wire-haired miniature dachshund	M (n)	Diarrhoea	7	Yes	No
Mixed breed	M (n)	Severe immune-mediated thrombocytopenia	7	No	No
French bulldog	F (n)	Haematuria	10	No	No
Yorkshire terrier	F (n)	Occasional diarrhoea	40	Yes	Yes
		Worsening skin condition			
Akita inu	F	Itch worsening	5	No	No
Mixed breed	M	Important itch worsening	7	Yes	No
Alpenlaendische dachsbracke	F (n)	Sudden itch worsening, excoriation appearance, fever	50	No	Yes
Boston terrier	F (n)	Erythema worsening of legs and neck	54	No	Yes

that reported in an open-label long-term study of oclacitinib, where 38.5% was achieved.[47]

Eighty percent of dogs had improved lesion scores by the end of the study. To the best of the authors' knowledge this is the first study to use the CADLI scoring system to evaluate treatment interventions in cAD, previous trials having relied on the original CADESI or one of its modified/updated versions. The choice of CADLI over other scales was based on its speed, simplicity and responsiveness to change. On this basis, the reduction in skin lesion severity and the percentage of dogs whose lesion scores improved ≥50% were found here to be similar to that of other therapies for cAD (see Table S1 in Supporting information).[35–52] Moreover, the mean percentage reduction observed here is notably higher than that previously recorded for a placebo.[34,37,38,46,48] Importantly, more than half of the dogs finishing the study had a CADLI score below 5. Based on validated disease severity thresholds for CADLI,[4] the five-point benchmark predicts that an overall assessment equal to 0 is consistent with clinical remission. Thus 8 weeks of PEA-um treatment induced the remission of skin lesions in 62% of dogs with moderate cAD. Furthermore, the present study indicates that the greater the baseline severity of lesions, the more robust was the effect of PEA-um. This last finding is clinically interesting and differs from that reported for ciclosporin, where no significant correlation was found between baseline lesion score and percentage of improvement.[35]

Pruritus has an important impact on QoL in canine dermatology.[53] The assessment of pre- and post-treatment QoL scores with validated scales is a valuable tool for monitoring owner satisfaction in studies on treatment interventions for cAD.[11] Using a validated questionnaire,[6] we evaluated the effect of PEA-um on QoL. Both total and subcluster QoL scores decreased significantly in response to treatment. To the best of the authors' knowledge QoL outcome has not been evaluated previously, except for a validation study[7] and a study on a budesonide leave-on-conditioner, where QoL was assessed using an nonvalidated scale.[54] Unlike the former study highlighting a higher mean improvement for QoL1 compared to QoL2,[7] the current data show that the two QoL subclusters improved to a similar extent in response to treatment. Because QoL1 is dog-related whereas QoL2 is owner-related, our findings suggest that PEA-um benefits both parties equally.

The low incidence of AEs seen in this study is consistent with preclinical[18] and clinical studies of PEA in companion animals[21,29] and humans.[18] In the present study only 11 out of 160 dogs (7%) had an AE, a lower proportion than seen with currently used cAD therapies, whose AE rate ranges between 50 and 76% for ciclosporin,[37,44,49] 50% to 80% for corticosteroids[39,44] and 50% to 59% for masitinib.[41,48] Only studies recording all AEs, regardless of causality, were used for comparison. Indeed, many studies detail the proportion of AEs for "reason subclusters" (withdrawals or worsening of clinical signs are considered different issues from adverse effects)[36,39,40] and others the percentage of a particular AE (e.g. emesis, diarrhoea),[32,35,51] thus making impossible a direct comparison with the global AE rate. The percentage of AEs possibly associated with treatment were 2.5% of dogs treated with PEA-um, compared to 24% and 7% for ciclosporin and oclacitinib, respectively.[36,43] The present data support the safety profile of PEA-um.

We have to acknowledge the major limitations of our study: the open-label and uncontrolled design, and multicentre nature. Although the latter feature was chosen to allow recruitment of a sufficient number of subjects to satisfy the trial objective within a reasonable time-frame, we are well aware that having numerous investigators may potentially impact the homogeneity of treatment evaluation. In reality, only the assessment of lesions could be influenced by this limitation, all other outcomes being evaluated by the owner. To limit evaluation heterogeneity, clinicians underwent a training period prior to enrolling animals in order to familiarize themselves with the CADLI data-capture form and the lesion photographic guide provided with the original description of this scoring system.[4] Moreover, the large sample size tends to minimize variability induced by the multi-centre nature of the study.

Notwithstanding the above limitations, our findings suggest that PEA-um, within a multifaceted and integrated therapeutic approach for cAD, may be a promising treatment for dogs with moderate atopic dermatitis and moderate pruritus, with consequent improvement in QoL.

Acknowledgements

The authors are grateful to Stephen D. Skaper (Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy) for his valuable help in English language editing and greatly appreciated scientific advice.

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Supporting Information

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

Table S1. Clinical results of palmitoylethanolamide (PEA)-um compared with commonly used drugs for cAD.

Résumé

Contexte – Le palmitoyléthanolamide est un lipide bioactif naturel, produit à la demande par les cellules exposées à des dommages. Le palmitoyléthanolamide est connu pour contrer l'inflammation, le prurit et la douleur.

Objectifs – Le but de cette étude de 8 semaines était d'évaluer l'efficacité du palmitoyléthanolamide ultra-micronisé, oral (PEA-um) chez les chiens atteints de dermatite atopique modérée.

Sujets – Les cliniciens de 39 cliniques vétérinaires ont inclus 160 chiens avec une dermatite atopique non saisonnière et un prurit modéré.

Méthodes – Cette étude était ouverte et multicentrique. A jour 0 (D0) et 56 (D56), les propriétaires ont évalué le prurit à l'aide d'une échelle visuelle analogue (VAS) et ont rempli un questionnaire de Qualité de Vie (QoL). Les vétérinaires ont évalué la sévérité des lésions cutanées à l'aide du CADLI (Canine Atopic Dermatitis Lesion Index).

Résultats – Le score de prurit VAS moyen diminuait de 5.7 _ 0.08 cm (écart 3.8–7.9 cm) à 3.63 _ 0.19 cm (écart 0.1–9.2 cm) ($P < 0.0001$). A D56, 58% des chiens montraient une réduction de plus de 2 cm du score initial et 30% montraient un prurit absent à très modéré (VAS $\leq$ 2 cm). Le CADLI total moyen à D56 diminuait significativement ($P < 0.0001$); pour 62% des chiens, ce score atteignait une valeur dans les intervalles de rémission ($\leq$5). Le score de QoL moyen était significativement diminué ($P < 0.0001$) avec 45% des chiens atteignant des valeurs de QoL décrites pour les chiens sains. La tolérabilité était bonne à excellente avec seulement quatre chiens rapportant des effets indésirables associés au traitement.

Conclusions et importance clinique – PEA-um semble être efficace et sûr dans la diminution du prurit et des lésions cutanées et pour améliorer la QoL des chiens atteint de dermatite atopique modérée et de prurit modéré.

Resumen

Introducción – la palmitoiletanolamida es un líquido natural bioactivo producido bajo demanda de células expuestas y dañadas. La palmitoiletanolamida controla la inflamación, el picor y el dolor.

Objetivo – el propósito de este estudio de ocho semanas fue evaluar la eficacia de un producto oral ultra micronizado de palmitoiletanolamida (PEA-um) en perros con dermatitis atópica moderada.

Animales – veterinarios de 39 clínicas admitieron 160 perros en el estudio con dermatitis atópica no estacional y prurito moderado

Métodos – este fue un estudio multicéntrico abierto. En los días cero (D0) y 56 (D56) los propietarios evaluaron el prurito con una escala análoga visual (VAS) y completaron un cuestionario validado de calidad de vida (QoL). Los veterinarios valoraron la severidad de las lesiones de la piel utilizando el índice de lesiones de dermatitis atópica canina (CADLI).

Resultados – el prurito medio con la VAS disminuyó de 5,7 _ 0,08 cm (rango 3,8–7,9 cm) a 3,63 _ 0,19 cm (rango 0,1–9,2 cm) ($P < 0{,}0001$). Al D56, 58% de los perros mostraron una reducción mayor de dos centímetros del valor basal, y un 30% mostraron prurito ausente a muy ligero (VAS $\leq$ 2 cm). La mediana total de CADLI a D56 disminuyó significativamente ($P < 0{,}0001$); en un 62% de perros este valor alcanzó rango de remisión ($\leq$5). La mediana total del valor QoL estuvo significativamente disminuida ($P < 0{,}0001$) con un 45% de perros alcanzando valores de QoL descritos para animales sanos. La tolerabilidad fue buena a excelente con solo cuatro perros mostrando efectos adversos reversibles.

Conclusiones e importancia clínica – la PEA-um parece ser un tratamiento efectivo y seguro para reducir el prurito y las lesiones de la piel, para mejorar el QoL en perros con dermatitis atópica moderada y moderado prurito.

Zusammenfassung

Hintergrund – Palmitoylethanolamide ist ein natürlich auftretendes bioaktives Lipid, welches nach Bedarf von Zellen, die der Zerstörung ausgeliefert sind, produziert wird. Es ist dokumentiert, dass Palmitoylethanolamide Entzündung, Juckreiz und Schmerz entgegenwirkt.

Ziel – Das Ziel dieser 8-wöchigen Studie war eine Evaluierung der Wirksamkeit eines *per os* verabreichten ultra-zerkleinerten Palmitoylethanolamide (PEA-um) bei Hunden mit moderater atopischer Dermatitis.

Tiere – Kliniker aus 39 Tierklinken nahmen 160 Hunde mit nicht saisonaler atopischer Dermatitis und moderatem Juckreiz in die Studie auf.

Methoden – Es handelte sich um eine offene Multi-center Studie. An den Tagen 0 (D0) und 56 (D56) evaluierten die BesitzerInnen mittels Visual Analog Scale (VAS) den Juckreiz und füllten einen validierten Fragebogen bezüglich der Lebensqualität (QoL) aus. TierärztInnen beurteilten den Schweregrad der Hautveränderungen mittels Canine Atopic Dermatitis Lesion Index (CADLI).

Ergebnisse – Die durchschnittlichen Juckreiz VAS Werte nahmen von 5,7_0,08cm (Breite 3,8-7,9 cm) auf 3,63_0,19 cm (Breite 0,1-9,2 cm) ab (P<0,0001). Am D56 zeigten 58% der Hunde eine Verkleinerung im Ausmaß von mehr als 2 cm vom Ausgangswert und 30% zeigten keinen-bis sehr milden Juckreiz (VAS ≤ 2cm). Der durchschnittliche Gesamt CADLI am D56 hatte signifikant abgenommen (P<0,0001); bei 62% der Hunde erreichte diese Bewertung einer Wert im Bereich der Remission (≤5). Der durchschnittliche QoL Wert war signifikant vermindert (P<0,0001) wobei 45% der Hunde QoL Werte erreichten, wie sie für gesunde Tiere beschrieben sind. Die Toleranz war gut bis ausgezeichnet, da nur bei vier Hunden behandlungsabhängige reversible Nebenwirkungen auftraten.

Schlussfolgerungen und klinische Bedeutung – PEA-um scheint wirksam und sicher zu sein bei der Reduzierung von Juckreiz und Hautveränderungen, sowie bei der Verbesserung der QoL bei Hunden mit moderater atopischer Dermatitis und moderatem Juckreiz.

要約

背景 — パルミトイルエタノールアミドは損傷を受けた細胞の要求に応じて産生される天然性生物活性脂質である。パルミトイルエタノールアミドは痒みや痛みの炎症を中和すると実証されている。

目的 — この8週間の調査の目的は、中程度のアトピー性皮膚炎のイヌにおける経口超微粒パルミトイルエタノールアミド(PEA-um)の効果を評価すること。

供与動物 — 39の獣医診療所の臨床医が非季節性アトピー性皮膚炎と診断し、中程度の痒みを示す160頭のイヌを組み入れた。

方法 — これは多施設非盲検試験である。0日目(D0)および56日目(D56)に、飼い主はビジュアルアナログスケール(VAS)で痒みを評価と正当性が認められている生活の質(QoL)のアンケートを記入した。獣医師はseverity of skin lesions using the Canine Atopic Dermatitis Lesion Index (CADLI)を評価した。

結果 — 平均そう痒VASスコアは5.7 _ 0.08 cm (範囲 3.8–7.9 cm) から 3.63 _ 0.19 cm (範囲 0.1–9.2 cm) (P < 0.0001)に減少した。D56には58%のイヌが基準から2cm以上の減少を示し、30%はそう痒なしから非常に軽度のそう痒(VAS ≤ 2 cm)を示した。D56の平均総CADLIは有意に減少し(P < 0.0001)、62%のイヌではこのスコアが寛解範囲(≤5)に到達した。平均総QoLスコアは有意に減少し(P < 0.0001)、45%のイヌは健康な動物とみなせるQoL値に到達した。忍容性は治療に関連した可逆性の有害事象が報告された4頭以外では、良好から非常によかった。

結論および臨床的な重要性 — PEA-umは中程度のアトピー性皮膚炎および中程度のそう痒を示すイヌにおいて、そう痒と皮膚病変の減少やQoLの改善に関して効果的で安全であるように思われた。

摘要

背景 — 十六酰胺乙醇是一种具有活性的天然脂类,由损伤细胞产生。十六酰胺乙醇已被证明能够对抗炎症、瘙痒和疼痛。

目的 — 这项为期8周的研究,目的为评估中度异位性皮炎的患犬,口服超微化十六酰胺乙醇(PEA-um)的疗效。

动物 — 来自39家兽医诊所的160只就诊犬,均为非季节性异位性皮炎,并呈中度瘙痒。

方法 — 这是一项多中心开放性实验。在第0天(D0)和56天(D56),动物主人通过直观类比标度(VAS),对瘙痒进行评估,并完成一份有效的生活质量(QoL)调查表。兽医通过犬异位性皮炎病变指数列表(CADLI),评估皮肤病变的严重程度。

结果 — VAS平均瘙痒分数从5.7 _ 0.08 cm (范围 3.8–7.9 cm)降低到3.63 _ 0.19 cm (范围 0.1–9.2 cm) (P < 0.0001)。在第56天时,58%的犬比基线降低超过2cm,30%的犬表现出时有时无的轻度瘙痒(VAS ≤ 2 cm)。在D56,平均总CADLI显著降低(P < 0.0001);62%的犬分数能够达到缓解范围(≤5)。在患犬总生活质量分数平均值显著降低(P < 0.0001)的情况下,45%的犬QoL值达到健康动物标准。报告中显示,犬对此项治疗的耐受性好至非常好,仅有4只犬出现了可逆的不良反应。

总结和临床意义 — PEA-um可安全有效地减轻瘙痒和皮肤损伤,并且能够改善中度异位性皮炎和中度瘙痒患犬的QoL。