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Effect of dietary supplementation with ultramicronized palmitoylethanolamide in maintaining remission in cats with nonflea hypersensitivity dermatitis: a double-blind, multicentre, randomized, placebo-controlled study

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Background – Feline nonflea hypersensitivity dermatitis (NFHD) is a frequent cause of over-grooming, scratching and skin lesions. Multimodal therapy often is necessary.

Hypothesis/Objectives – To investigate the efficacy of ultramicronized palmitoylethanolamide (PEA-um) in maintaining methylprednisolone-induced remission in NFHD cats.

Animals – Fifty-seven NFHD cats with nonseasonal pruritus were enrolled originally, of which 25 completed all study requirements to be eligible for analysis.

Methods and materials – Cats were randomly assigned to PEA-um (15 mg/kg per os, once daily; n = 29) or placebo (n = 28) while receiving a 28 day tapering methylprednisolone course. Cats responding favourably to methylprednisolone were then administered only PEA-um (n = 21) or placebo (n = 23) for another eight weeks, followed by a four week long treatment-free period. Cats were maintained in the study until relapse or study end, whichever came first. Primary outcome was time to relapse. Secondary outcomes were pruritus Visual Analog Scale (pVAS), SCORing Feline Allergic Dermatitis scale (SCORFAD) and owner Global Assessment Score (GAS).

Results – Mean relapse time was 40.5 days (±7.8 SE) in PEA-um treated cats (n = 13) and 22.2 days (±3.7 SE) for placebo (n = 12; $P = 0.04$). On Day 28, the severity of pruritus was lower in the PEA-um treated cats compared to placebo ($P = 0.03$). Mean worsening of pruritus at the final study day was lower in the PEA-um group compared to placebo ($P = 0.04$), whereas SCORFAD was not different between groups. Mean owner GAS at the final study day was better in the PEA-um than the placebo-treated group ($P = 0.05$).

Conclusion and clinical importance – Ultramicronized palmitoylethanolamide could represent an effective and safe option to delay relapse in NFHD cats.

Introduction

Feline allergic dermatitis (also referred to as hypersensitivity dermatitis, HD) is a chronic, noncurable inflammatory skin disease and frequent cause of over-grooming, scratching and skin lesions. It represents a challenge for the veterinary practitioner in terms of both diagnosis and treatment.[1] Although in dogs atopic dermatitis (AD) has been recognized and well-described both clinically and immunologically, research in feline skin allergy is still in its infancy.[2,3] Flea and insect bite hypersensitivity and adverse food reactions are recognized, whereas environmental allergy (nonflea, nonfood HD (NFNFHD), also called feline AD or atopic-like syndrome) is suspected when the former two are excluded, and remains incompletely defined.[3,4] The term "Nonflea hypersensitivity

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Conflicts of Interest: Chiara Noli is a consultant for Innovet Italia Srl, and for Zoetis, Elanco, CEVA and ICF. Alda Miolo and Cristina Medori are employees of Innovet Italia Srl. Maria Federica della Valle 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.

dermatitis" (NFHD) encompasses cats with NFNFHD and with nonflea-food HD and has defined, validated diagnostic criteria.[4] Cats with NFHD exhibit pruritus and at least one of the following patterns: head and neck excoriations/pruritus, self-induced alopecia, eosinophilic diseases (eosinophilic plaques or granulomas, lip ulcerations) or miliary dermatitis. Clinical manifestations are not as anatomically site-specific as in dogs and none of these reaction patterns is pathognomonic for NFHD in cats.[3,4]

Among the therapeutic approaches used for NFHD, glucocorticoids (especially in a tapering-dose regimen) are often highly effective and widely used.[5] Care is recommended when administering corticosteroids to cats, because of potential adverse effects, especially with long-term use (including diabetes).[5–7] Steroids are accepted as first-line therapy for short treatment courses or seasonal pruritus; ideally alternatives should be sought for long-term therapy, where possible using a multimodal approach.[6] A multimodal treatment approach aims to combine different therapies to decrease pruritus and inflammation below the threshold of clinical signs, and concurrently allow for dosage reduction of anti-inflammatory or immunosuppressive drugs.

Palmitoylethanolamide (PEA) is a naturally occurring lipid compound with antiallergic and anti-inflammatory effects.[8,9] At the cellular level, PEA is known to down-modulate cells (including skin mast cells, keratinocytes, macrophages and pro-inflammatory T cells)[10–13] which are characteristic of feline allergic inflammation.[14–16] A pilot study on cats with eosinophilic granuloma and eosinophilic plaque showed that a 30-day oral treatment with co-micronized PEA improved erythema, pruritus and alopecia, and reduced the extension and severity of skin lesions in >60% of treated cats.[17]

Our hypothesis was that PEA-um could be usefully combined with a short-course standard corticosteroid therapy and delay relapse after steroid withdrawal in cats with NFHD.

Methods and materials

Study design

This study was designed as a double-blind, placebo-controlled, multicentre randomized clinical trial (RCT). 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 cats to participate in the study and were free to withdraw their pet at any time without prior notice.

Animals

Twenty-two Italian clinics with clinicians who were members of the "Skinalia Clinical Research Group" participated in the study. Client-owned cats, 12 months of age or older, of any breed or sex, with moderate-to-severe nonseasonal pruritus and NFHD were selected, based on published diagnostic criteria for feline NFHD.[4] "Nonseasonal pruritus" was defined as either (i) persistent pruritus lasting more than six months or (ii) waxing and waning pruritus lasting for longer than 12 months, taking into consideration that the pollen season never exceeds four months in the country in which the study was conducted.

To be included in the study, a minimum score of 4 cm on a pruritus Visual Analog Scale (pVAS) with behavioural descriptors (see Clinical Evaluation Scoring below) was required. Moreover, cats had to fulfill the list of inclusion and exclusion criteria detailed in Table 1.

Randomization and blinding

Investigators and owners were blinded to treatment. Cats were randomized according to a computer-generated list with a 1:1 ratio and four-subject block size. Group allocation also took into consideration a stratification based on the prevalent clinical presentation in order to minimize heterogeneity of baseline covariates. Presentation patterns were the following: head and neck pruritus, self-induced alopecia, miliary dermatitis and/or lesions of the eosinophilic granuloma complex (including eosinophilic plaque, eosinophilic granuloma and lip ulceration).

Study product

Palmitoylethanolamide (also known as Palmidrol INN, International Non-proprietary Name) was provided in ultra-micronized form (PEA-um) and formulated as an oral suspension at a concentration of 60 mg/mL and supplied in 130 mL bottles with adaptor and oral graduated syringe. The placebo contained vehicle only and was indistinguishable from the active product for rheological, organoleptic, dosage and packaging features. PEA-um and placebo were administered once a day by the owner from the beginning to the end of the study, with the exception of follow-up. Owners were instructed to administer the oral suspension according to the following directions: (i) shake well; (ii) insert the syringe into the bottle adaptor; (ii) turn bottle upside down; (iii) pull plunger to extract the required dose (1 mL in cats ≤4 kg and 1.5 mL in cats >4 kg); (iv) remove syringe; (v) administer directly into the cat's mouth.

Study protocol

The study was organized in the following phases (detailed timeline in Figure 1).

1. Phase 1–Four weeks, days 0–28. At the beginning of this phase, cats were randomized to PEA-um (about 15 mg/kg once daily per os) or placebo, and treatment was started accordingly. All cats also received a two week methylprednisolone p.o. treatment course (Medrol Vet, Zoetis; Rome, Italy; 4 mg once daily for cats ≤5 kg; 6 mg once daily for cats >5 kg). On Day (D)14, cats fulfilling at least two of three improvement criteria (see Figure 1) had methylprednisolone administration reduced to every other day. If, at the end of the following two weeks, the skin disease was still under control (please refer to D28 improvement/maintenance criteria in Figure 1) methylprednisolone was withdrawn and the cat moved into Phase 2. Otherwise, it exited the study and was considered a methylprednisolone nonresponder.
2. Phase 2–Eight weeks, days 28–84 (maximum duration). During this phase, cats were maintained on PEA-um or placebo only and kept in the study until relapse occurred (please refer to the final visit worsening criteria in Figure 1).
3. Follow-up–Four weeks, days 84–112 (maximum duration). Cats that did not relapse during Phase 2 entered a follow-up period until the owner judged the clinical condition "much worse" or until the study end (Week 16), whichever came first. No treatment was allowed during this phase.

Telephone interviews at regular intervals (Figure 1) were performed by the study monitor in order to verify compliance with the study protocol.

Clinical evaluation scoring

Clinical evaluation was performed at days 0, 14, 28 and D-final (relapse or D84; Figure 1) with the following scoring systems.

Table 1. Eligibility criteria for cats to be enrolled in the study

Inclusion criteria
Age ≥ 12 months
Weight > 3 kg
Diagnosis of HD (fulfilment of five of eight Favrot's diagnostic criteria)[4]
Nonseasonal pruritus (both persistent pruritus lasting more than six months, and waxing and waning pruritus lasting for >12 months)
Moderate-to-severe pruritus (pVAS > 4 cm)
Regularly receiving antiparasitic prophylaxis, before inclusion (at least four weeks) and for the whole study duration
Maintaining the same diet and environment before entering (at least four weeks) and during the study
Owner's statement to comply with the protocol and signed written informed consent
Exclusion criteria
Clinical evidence of bacterial, fungal, parasitic infections of the skin/ears; e.g. Malassezia dermatitis, dermatophytosis, demodicosis, otodectic mange (ear mites), notoedric mange (feline scabies) and cheyletiellosis
Pruritus from any origin but Hypersensitivity Dermatitis
Clinical contraindications to corticosteroid treatment
Pregnant or lactating cats
Ongoing dietary restriction-provocation trials
Any concomitant treatment (e.g. antihistamines, essential fatty acids, ciclosporin, oclacitinib, antibiotics)
Allergen specific immunotherapy begun <12 months before inclusion

1. Pruritus VAS (pVAS); an unvalidated owner-assessed feline scratching and licking Visual Analog Scale with behavioural descriptors (Figure 2); adapted from a scale for dogs.[18] Given that a single best measure for the evaluation of pruritus severity, regardless of how the particular cat manifested signs of pruritus, was needed for analysis purposes, the higher of the two registered scores (licking or scratching) was considered at any time point. This was then substantiated by correlation analysis (see Statistical procedures below).
2. SCORing Feline Allergic Dermatitis (SCORFAD) scale; a validated tool for the assessment of skin lesion extension and severity in cats with HD.[19]
3. Global Assessment Score (GAS); a 0–3 global owner-assessed score (compared to the previous visit, the clinical condition of my cat as pertaining to severity of pruritus and skin lesions is: 0, improved; 1, unchanged; 2, worse; or 3, much worse).

Outcomes and efficacy variables

Primary outcome was the time-to-relapse, defined as days needed for either lesions, pruritus or global condition to worsen after methylprednisolone withdrawal. In particular, relapse was determined if the cat fulfilled at least two of the following criteria:

1. 2-point or more increase of SCORFAD and score ≥4
2. 2-cm or more increase for pVAS
3. GAS = 3

Secondary outcomes were SCORFAD, pVAS and GAS scores at each time point.

The efficacy variables were (i) time-to-relapse, (ii) the change from D28 to the final visit in pVAS and SCORFAD scores, and (iii) the final visit GAS.

Tolerability

Tolerability was assessed by monitoring 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". Any AE was recorded whether or not it was considered to be related to treatment. All untoward effects that occurred during the study were recorded, together

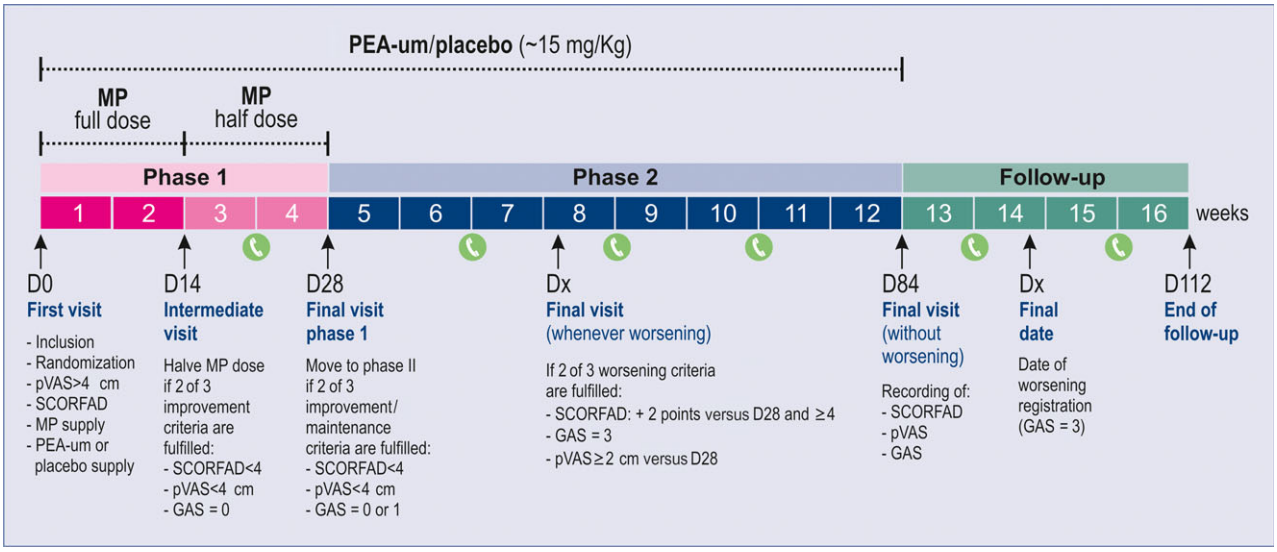

Figure 1. Timeline of the study.The day of worsening (Dx) was recorded provided that the investigator confirmed the fulfilment of worsening criteria at the clinical visit.
If the skin condition got worse during follow-up, the owner assessment was considered sufficient. GAS, owner Global Assessment Score; MP, methylprednisolone; pVAS, pruritus Visual Analog Scale; SCORFAD, SCORing Feline Allergic Dermatitis scale.

with their onset, severity and perceived causal relationship with the trial intervention.

Statistical procedures

Data were analysed using SAS v9.2 (SAS Institute, Cary; NC, USA). The level of significance was set at $P < 0.05$. Demographic analyses were performed on all enrolled subjects, using descriptive statistics (mean ± standard deviation, SD). When analyses on means were carried out (for primary and secondary outcomes) mean ± standard error (SE) were used. The analysis of time-to-relapse following methylprednisolone withdrawal was performed through the Kaplan–Meier survival analysis. The log-rank test was used to evaluate the difference between time-to-relapse values of the two treatment groups.

Kaplan–Meier analysis is based on the assumption that censoring (i.e. the condition in which the observation is incomplete) is independent from the likelihood of developing the event (which in this study was the relapse).[20,21] If the assumption is violated then the Kaplan–Meier estimator may be biased yielding incorrect inferences; furthermore, subsequent analysis such as log-rank test also are inconsistent.[21] Where the censoring time is positively correlated to the time-to-event, the latter is overestimated with a ceiling effect to the end of the study period. In order to avoid overestimation, the analysis of the complete dataset (without censoring) was performed having verified that (i) the censoring pattern was not related to treatment (Fisher's exact test and Student's *t*-test were used to this end); (ii) factors other than treatment (i.e. reaction pattern, pruritus presentation and time from the first diagnosis) did not influence time-to-relapse (stepwise procedure on Cox proportion hazard model was applied accordingly); and (iii) secondary outcomes did not differ between treatment groups on censored subjects (the same model was used as in the main analysis on relapsed cats, see below).[22]

All of the analyses pertaining to secondary outcomes were performed on complete observations (relapsed cats) and time-to-relapse. This was done both for homogeneity reasons and because analyzing the whole sample would have biased the effect, resulting in an overestimation. Changes in pVAS and SCORFAD scores following methylprednisolone withdrawal (between D28 and final visit) were analyzed using the generalized linear mixed model (GLMM). GLMM was used as no outliers were observed at a visual inspection of the data. The fixed effects in the model were treatment group, reaction pattern, pruritus presentation (waxing and waning/persistent) and onset (time from the first HD diagnosis). The random effect in the model was the animal.

Pearson's correlation was used to analyze the association between pVAS licking and scratching scores and between the higher of these sub-scores and SCORFAD. The Wilcoxon signed rank test was used to analyze the effect of treatment on GAS at the final visit.

Results

Animals

Between March 2017 and February 2018, 57 cats were included. Thirty-two were females and 25 males, all neutered except two females and two males. The mean weight was 4.9 kg (SD: 1.1; range 3.1–8.0) and mean age 5 years and 2 months (SD: 3.7 years, range 1–15). Domestic short hair was the most represented breed (n = 49, 86%); other breeds were two domestic long hair and one each of Chartreux, Thai, Devon rex, British shorthair, Scottish fold and Cornish rex. All cats but one were housed indoors only. The mean disease duration before study entry was 2.1 years (SD: 1.8; min 0.5–max 8.4). In 16% of cases, adverse reaction to food was excluded by means of a negative response to an elimination diet. Due to unwillingness of the owners to administer – or of the

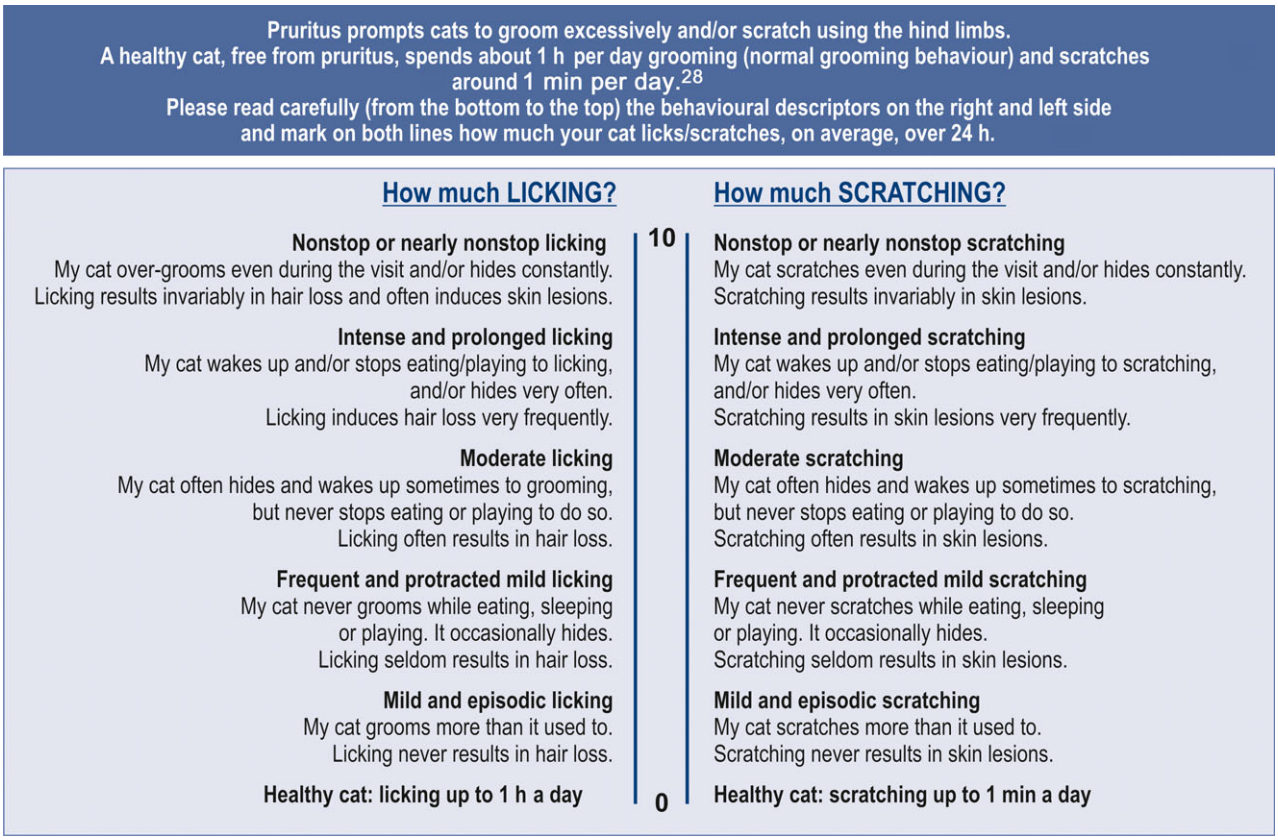

Figure 2. Dual feline pruritus Visual Analog Scale (pVAS) (courtesy of Silvia Colombo)

cat to eat – an elimination diet, food-induced HD was not excluded in the remainder.

Basal clinical presentation

Twenty-eight cats (49%) had a single reaction pattern, the remaining (51%) presented with multiple associated patterns, five of which had three concomitant patterns. Symmetrical self-induced alopecia was the most frequent clinical pattern (58%, n = 33, 22 of which presented the pattern as prevalent), followed by head and neck pruritus (53%, n = 30, 21 of which presented the pattern as prevalent). The relative frequency of clinical patterns at presentation is depicted in Figure 3.

Most of the study cats (n = 40, 70%) presented with waxing and waning nonseasonal pruritus lasting for over 12 months, and the remainder had persistent pruritus of over six months duration. The majority of cats (n = 46, 81%) presented a prevalent manifestation of pruritus (i.e. licking higher than scratching score or vice versa). There was a lack of correlation between the two scores ($r = -0.0075$). The higher of the two sub-scores correlated better to SCORFAD score ($r = 0.2262$) compared to the individual licking and scratching sub-scores ($r = 0.0529$ and $r = 0.1895$, respectively), and was thus used for all subsequent analyses.

Fourteen cats (24%) had mild-to-moderate pruritus (pVAS from >4 to 6 cm), 30 (53%) had moderate-to-severe pruritus (pVAS from >6 to 8 cm) and 13 (23%) had severe/very severe (pVAS > 8 cm). At baseline, no statistically significant difference was found in mean pVAS score between PEA-um and placebo groups (6.9 ± 0.30 cm and 7.3 ± 0.24 cm, respectively; $P = 0.22$). Moreover, mean pVAS scores were evenly distributed among clinical presentation patterns ($P = 0.53$), indicating that severity of pruritus was not associated with any particular clinical presentation.

The basal SCORFAD score ranged between 2 and 4 in 26% (n = 15) of cats, 5 and 6 in 35% (n = 20) and was >6 in 39% of the study cats (n = 22). The mean severity of skin lesions at baseline was evenly distributed between PEA-um and placebo groups (mean SCORFAD score 6.3 ± 0.37 and 6.0 ± 0.54, respectively; $P = 0.87$) and among clinical presentation patterns ($P = 0.81$), thus showing the lack of association between lesion severity and clinical presentation patterns.

Outcome analyses

Figure 4 illustrates the study flow chart including the number of cats remaining in the study at each phase and the reasons for dropping out. As shown in the figure, there was a large proportion of right censoring, with almost 40% of cats remaining relapse-free by the end of the study, indicating that censoring time was not independent of relapse time. Complete data analysis (on relapsed cats, n = 25; 12 in placebo, 13 in PEA-um groups) was performed accordingly for each outcome variable, after having verified the following necessary assumptions: (i) there was no statistically significant difference of censored data ratio and mean censoring time between groups ($P = 0.56$ Fisher's exact test and $P = 0.46$ Student's t-test, respectively); (ii) the stepwise

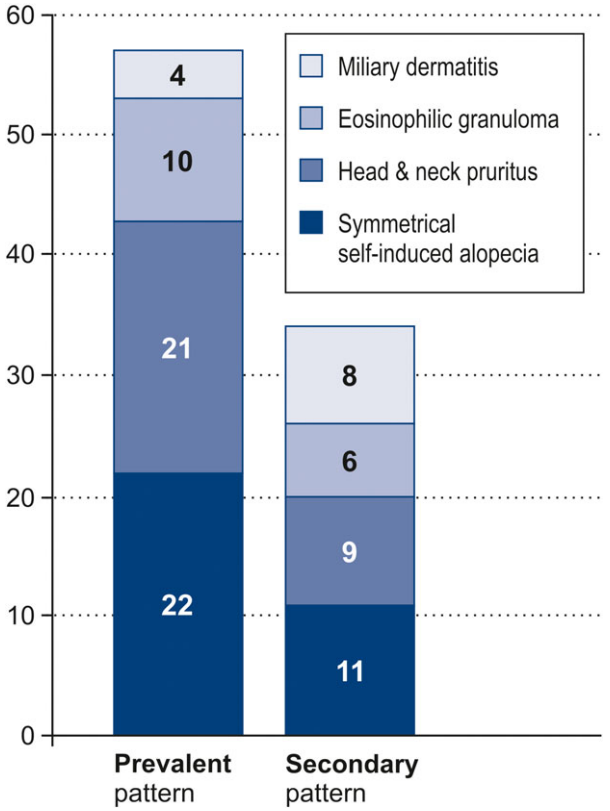

Figure 3. Numbers of cats and distribution of primary and secondary lesional patterns in cats with nonflea hypersensitivity dermatitis enrolled in the study.

procedure showed that none of the tested variables but treatment affected time-to-relapse ($P = 0.04$, Cox proportion hazard model); and (iii) secondary outcomes did not differ between treatment groups on censored cats (no statistically significant difference at GLMM; see Pruritus and Skin lesions sections below). Eighty percent of the relapsed cats (20 of 25) had relapse assessed upon both veterinarian's (SCORFAD) and owner's criteria (pVAS and/or GAS); nine in PEA-um, 11 in the placebo groups. The remaining cats (n = 5; one in placebo, four in PEA-um treated groups) fulfilled the owner's criteria only.

Time-to-relapse

After methylprednisolone withdrawal, time-to-relapse in days was significantly longer in the PEA-um treated group compared to placebo ($P = 0.04$; Figure 5). In particular, one month after methylprednisolone withdrawal, 46.2% of PEA-um treated cats were still in the study compared to 16.7% of cats in the placebo group (Table 2). Six cats in the PEA-um group and 10 cats in the placebo group did not relapse.

Pruritus

By D28 (following four weeks of cotreatment with methylprednisolone and study product or placebo, depending on the treatment group) the severity of pruritus was significantly lower in PEA-um compared to placebo-treated cats (mean pVAS score 0.9 ± 0.22 cm versus 1.4 ± 0.50 cm; $P = 0.03$). As expected, pruritus

scores worsened ($P < 0.0001$) after methylprednisolone withdrawal (from D28 to final visit) regardless of the treatment group. However, pVAS worsened significantly less in the PEA-um group compared to the placebo group (Figure 6). In particular, the mean increase of pVAS score after methylprednisolone withdrawal was 3.5 ± 0.94 cm and 5.7 ± 0.39 cm in the PEA-um and placebo groups, respectively ($P = 0.04$). The effect of PEA-um was not affected by (i) clinical presentation pattern ($P = 0.90$), (ii) disease duration before study entry ($P = 0.88$) or (iii) pruritus presentation (waxing and waning, or persistent) ($P = 0.54$). In censored cats no statistically significant difference between PEA-um and placebo groups was found in the mean change of pVAS score after methylprednisolone withdrawal (−0.5 ± 0.79 cm and −1.1 ± 0.35 cm, respectively; $P = 0.51$).

Skin lesions

No difference was observed at D28 between the mean SCORFAD scores of the PEA-um and placebo groups (1.5 ± 0.46 and 1.1 ± 0.34, respectively; $P = 0.87$). Following methylprednisolone withdrawal, the increase of mean lesional score was 3.0 ± 0.81 in the PEA-um and 3.4 ± 0.58 in the placebo group, with no statistically significant difference between groups ($P = 0.70$). No difference was observed between groups in censored cats (−0.3 ± 0.57 and −0.3 ± 0.24 in the PEA-um and placebo groups, respectively, $P = 0.95$).

Owner-assessed GAS

At the final visit, the owners judged PEA-um to be superior to placebo in maintaining the effects obtained in their cats with methylprednisolone. In particular, 33% of the owners in the PEA-um group, but none in the placebo group, judged that the clinical condition of their cat at the final visit remained unchanged compared to the condition observed after the 28 day treatment course with methylprednisolone ($P = 0.05$).

Tolerability

Ten cats were reported to have had AEs during the study, six of which were observed during the first phase of the study (i.e. methylprednisolone co-administration). Four AEs were reported in the PEA-um group and six in the placebo group. A total of four cats, evenly distributed between treatment groups, were withdrawn due to AEs. None of them was considered serious. An overview of AEs, including the perceived causal relationship with the trial intervention, is summarized in Table 3.

Discussion

To the best of the authors' knowledge, this is the first double-blind RCT to demonstrate a significant effect of PEA on skin disease in cats. The Previous study that investigated the effect of PEA (as naïve or ultramicronized formulation) on pruritus of various origins and on skin

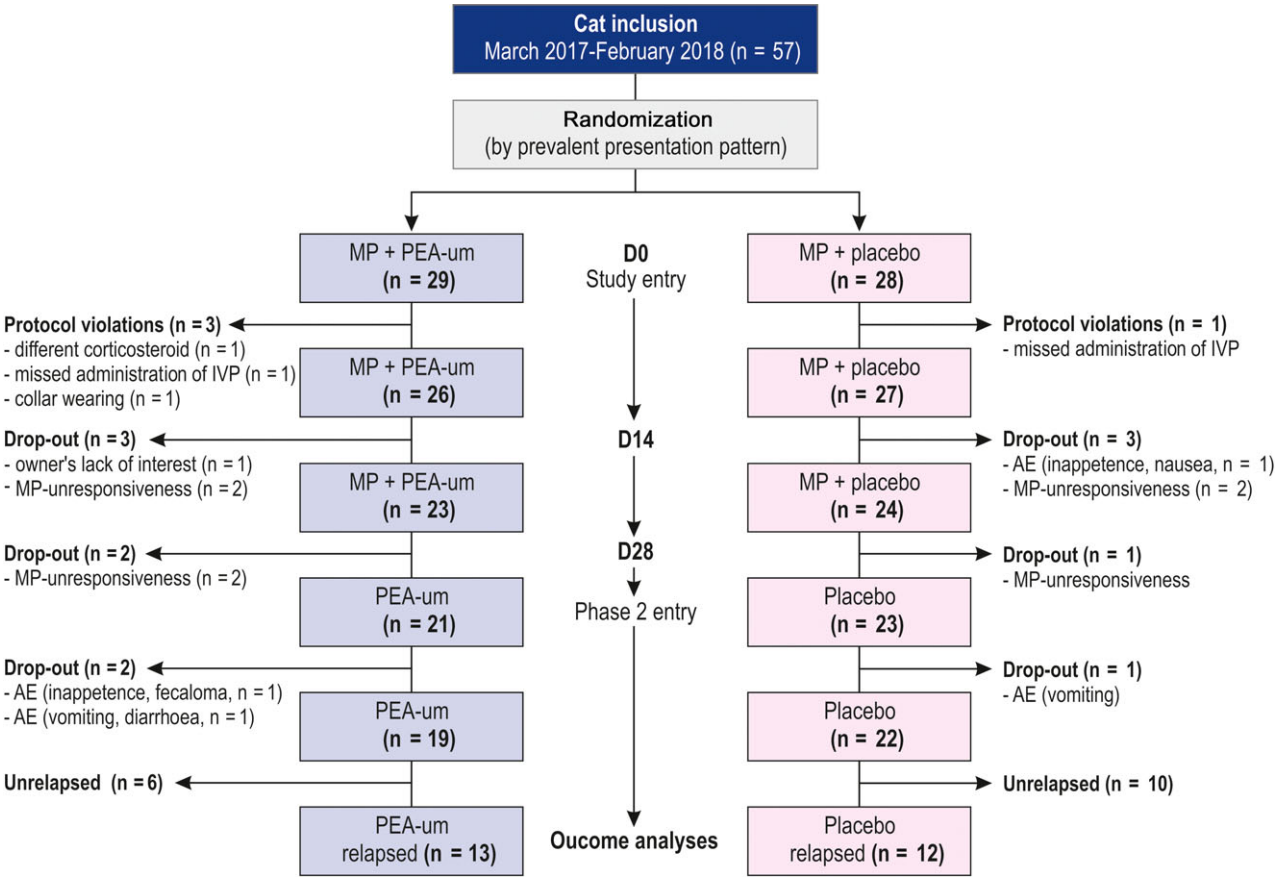

Figure 4. Flow chart of the study.
AE, adverse event; IVP, investigational product (either PEA-um or placebo); MP, methylprednisolone.

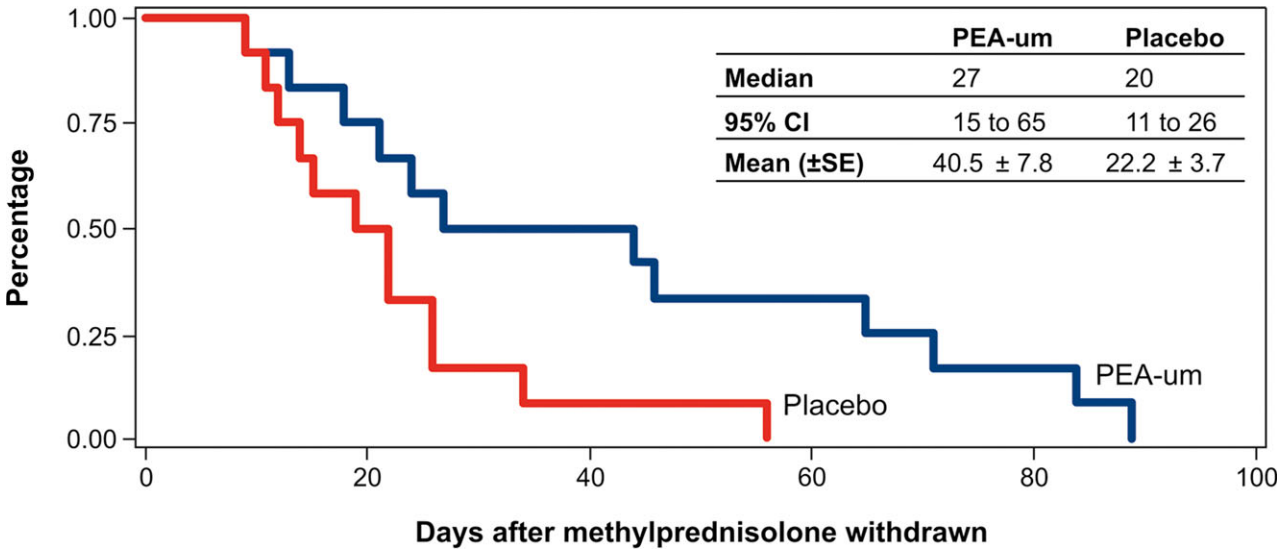

Figure 5. Survival plot for time-to-relapse in days for cats treated with methylprednisolone and either PEA or placebo.

lesions did not use a double-blind randomized controlled design.[17]

Palmitoylethanolamide is the parent molecule of aliamides and a congener of the endocannabinoid anandamide, with which it shares, at least in part, metabolic pathways and molecular targets.[10] PEA is locally produced "on demand" in several mammalian tissues as a pro-resolving agent able to boost resolution programmes during inflammation.[23,24] The antiallergic and anti-inflammatory effects of PEA are known to be mediated through several receptors including the peroxisome proliferator-activated receptor (PPAR)-α and cannabinoid type-1 and -2 receptors (CB1, CB2).[9,10] Interestingly, their expression is increased in the skin of cats with hypersensitivity dermatitis, suggesting that these receptors could represent new therapeutic targets for feline allergy.[25]

The present study showed that co- and post-administration of PEA-um enhanced the anti-pruritic effect of a short course of methylprednisolone treatment and was able to delay flares in cats with NFHD. This was (respectively) shown by the lower pruritus score both at D28 and at time of relapse, and the longer time to relapse in the PEA-um compared to the placebo-treated group. Interestingly, PEA-um resulted in a milder worsening of pruritus after methylprednisolone discontinuation regardless of the clinical presentation (i.e. type of lesions, disease duration, pruritus frequency). A small trial on allergic cats investigated the ability of methylprednisolone to maintain remission on a tapering regimen.[5] It was shown that after an 11 week long corticosteroid treatment period, six of 16 cats could be successfully maintained in remission with 25% of the effective induction dose, the others needing higher doses.[5] Likewise, an open label study on hydrocortisone aceponate spray showed that after eight weeks of daily treatment 40% of 10 cats with presumed allergic dermatitis required daily therapy to maintain remission and none of them could be switched to atwice-weekly regimen without relapsing.[26] In the present study, cats on PEA-um could be maintained relapse- and

Table 2. Number and percentage of cats with nonflea hypersensitivity dermatitis, treated with methylprednisolone and either PEA or placebo still, in the study at different time points after methylprednisolone withdrawal (D28).
Only cats that eventually relapes are considered in this table.

	PEA-um		Placebo	
Time	n	%	n	%
D28	13	100	12	100
Week 1	13	100	12	100
Week 2	11	84.6	8	66.7
Week 3	8	61.5	6	50
Month 1	6	46.2	2	16.7
Month 2	4	30.8	0	0

corticosteroid-free for a mean of six weeks, a significantly longer duration compared to placebo. This finding has implications within the clinical setting, owing to the chronic nature of feline allergic dermatitis, the inherent need for permanent antipruritic and anti-inflammatory treatment, and the time- and dose-related increase in the incidence of adverse effects due to standard-of-care medications, including but not limited to corticosteroids. As depicted in Table 3, only two PEA-um treated cats dropped out due to adverse events (both nonserious and gastrointestinal in nature), with the causal relationship between PEA-um treatment and AE being considered "possible" and "unlikely", respectively. It is worth noting that no particular difficulties were encountered by owners in orally administering the liquid suspension (i.e. PEA-um or placebo), only two cases of drooling being reported (Table 3). The fact that the formulation was designed to be palatable and the volume to administer was low (1 mL for a medium weight cat) might have helped to over come issues usually related to administering liquid formulations to cats.

Interestingly, PEA-um co-treatment during the four-week tapering regimen of methylprednisolone yielded a significantly lower pruritus score compared to placebo co-treatment. Although this was not a prespecified outcome of the study, and the effect was clinically small, it could

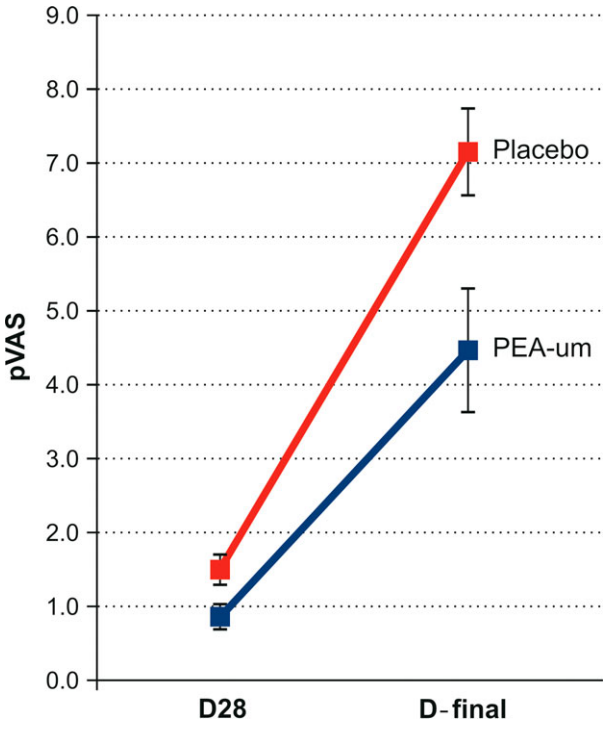

Figure 6. Change of pruritus severity of allergic cats in response to PEA-um or placebo treatment, after methylprednisolone withdrawal.

suggest a possible steroid-sparing effect of PEA-um, which would favour its use in a multimodal approach for prolonging time-to-flare in the feline allergic patient. This result, possibly due to the immunomodulatory action of PEA-um,[10,11] is worth further research.

The superior satisfaction of the owners of the PEA-um-treated cats over placebo, as expressed by the final visit GAS, supports the benefits of the aliamide in the management of feline NFHD.

The present study included some clinical information on feline NFHD, most of which agreed with previous reports. For example, the distribution of lesional patterns observed in the present study was similar to previous reports of NFHD, with self-induced symmetric alopecia and head and neck pruritus being the two most represented patterns in either studies (approximately 50–60% of the total registered patterns), whereas eosinophilic diseases and miliary dermatitis accounted for about 20–30%.[3,27] Interestingly, the present study has shown that the severity of either pruritus or skin lesion scores was not associated with any particular presentation pattern. To the best of authors' knowledge, this is an unprecedented finding and suggests that, at least in this study sample, different clinical patterns typical of feline NFHD do not differ with respect to the severity of pruritus and skin lesions. Moreover, it also implies that stratifying by pattern, as provided for in the present study, might not be required for future trials in the field.

A limitation of this study is the lack of exclusion of food allergy. Only 16% of the cats were diagnosed as NFNFHD. Unwillingness of the owners to administer the elimination diet and dietary preferences of individual cats were the major reasons contributing to the decision not to enforce elimination diet trials as part of the inclusion criteria. It is not definitively known whether food-induced allergic disease responds as well to oral glucocorticoids as nonfood-induced disease.[5] However, the study was randomized and all confounding effects, including possible food-induced allergy, were evenly distributed to both treatment groups. Moreover, the maintenance of the same diet for at least four weeks before entering and throughout the study (which was part of the inclusion criteria; Table 1) limited, at least in part, the possible impact of food allergy on the results. In any instance, the impact would be unquestionably negative and making any beneficial effect more difficult to achieve in both treatment groups.

A further limitation of this study is the small sample size. Although 57 cats with NFHD were originally included, only 25 (13 in the PEA-um group, 12 in the placebo group) were actually eligible for the analyses. Unresponsiveness to methylprednisolone (seven cases) and lack of relapse during the whole study duration (16 cases) were among the most important causes of sample size reduction. The high proportion of unrelapsed cats observed in the present study was unexpected and could have been caused by a seasonal pruritus of unusual duration or by an unexpectedly long spontaneous remission phase in waxing and waning pruritic cats.

The assessment of relapse in five of 25 cats was performed by the owners only, whose judgment was considered important for the evaluation of the clinical change, through GAS and pVAS. Pruritus is one of the main signs associated with NFHD; it is the first and easiest to be recognized by owners and is generally their chief complaint.

Table 3. Overview of adverse events, including number, type and perceived causal relationship with the trial intervention for cats treated with methylprednisolone (MP) and PEA. +MP = phase I, with methylprednisolone administration; −MP = phase II, without methylprednisolone administration.

	PEA-um		Placebo	
	Phase 1 (+MP)	Phase 2 (−MP)	Phase 1 (+MP)	Phase 2 (−MP)
Possible causal relationship				
Probable	1 (polyuria)	0	0	0
Possible	1 (vomiting)	1 (vomiting and diarrhoea)	2 (vomiting) and (drooling)	1 (vomiting)
Unlikely	0	1 (faecal impaction and inappetence)	1 (diarrhoea)	1 (vomiting)
Unclassifiable	0	0	1 (drooling and inappetence)	0
Total	2	2	4	2
Resulting in study exit	0	2	1	1
Serious	0	0	0	0

When considering the "maintenance of an effect", the owner is the first person to perceive a clinical change and thus the best subject to monitor the disease after steroid withdrawal.

In conclusion, the results of the present study show that dietary supplementation of PEA-um in cats with NFHD delayed relapse and improved the antipruritic effect of a short course of standard therapy. Although more work in a larger number of cats needs to be done, the findings suggest that PEA-um might be a valid option in the multimodal management of feline NFHD.

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Résumé

Contexte – La dermatite féline par hypersensibilité non liée aux puces (NFHD) est une cause fréquente de léchage, grattage et lésions cutanées. Un traitement multimodal est souvent nécessaire.

Hypothèses/Objectifs – Etudier l'innocuité du palmitoyléthanolamide ultramicronisé (PEA-um) pour le maintien de la rémission induite par la méthylprednisolone chez les chats NFHD.

Sujets – Cinquante sept chats NFHD, avec un prurit non saisonnier, ont été enrôlés initialement parmi lesquels, 25 ont complété tous les critères d'inclusion pour analyse.
Méthodes – Les chats ont été répartis au hasard pour PEA-um (15 mg/kg per os, une fois par jour; n = 29) ou placebo (n = 28) tout en recevant 28 jours de méthylprednisolone à doses dégressives. Les chats répondant favorablement à la méthylprednisolone ont ensuite reçus seulement du PEA-um (n = 21) ou un placebo (n = 23) pour huit semaines supplémentaires, suivies par quatre semaines sans traitement. Les chats ont été maintenus dans l'étude jusqu'à récidive ou la fin de l'étude. La durée de la récidive était le premier critère d'étude. Les critères secondaires étaient la pVAS (pruritus Visual Analog Scale), le SCORFAD (SCORing Feline Allergic Dermatitis scale) et le GAS (Global Assessment Score) des propriétaires.
Résultats – Le temps de rechute moyen était de 40,5 jours (±7.8 SE) pour les chats traités au PEA-um (n = 13) et 22.2 jours (±3.7 SE) pour le placebo (n = 12; P = 0.04). Au jour 28, la sévérité du prurit était plus faible pour les chats recevant du PEA-um comparé au groupe placebo (P = 0.03). L'aggravation moyenne du prurit au dernier jour de l'étude était plus faible dans le groupe PEA-um comparé au groupe placebo (P = 0.04), tandis que le SCORFAD n'était pas différent entre les groupes. Le GAS moyen des propriétaires au dernier jour de l'étude était meilleur dans le groupe PEA-um que dans le groupe placebo (P = 0.05).
Conclusion et importance clinique – Le palmitoyléthanolamide ultramicronisé pourrait représenter une option efficace et sure pour ralentir la rechute des chats NFHD.

Resumen
Introducción – la dermatitis por hipersensibilidad no causada por pulgas (NFHD) es una causa frecuente de excesivo aseo, rascado y lesiones cutáneas. a menudo es necesario un tratamiento multimodal.
Hipótesis/Objetivos – investigar la eficacia de la palmitoiletanolamida ultramicronizada (PEA-um) en el mantenimiento de la remisión inducida por metilprednisolona en gatos con NFHD.
Animales – originalmente se incluyeron 57 gatos con NFHD y prurito no estacional, de los cuales 25 completaron todos los requisitos del estudio para ser elegibles en el análisis final.
Métodos – los gatos se asignaron al azar a PEA-um (15 mg/kg por vía oral, una vez al día; n = 29) o placebo (n = 28) mientras recibían un ciclo de metilprednisolona de 28 días. A los gatos que respondieron favorablemente a la metilprednisolona se les administró solo PEA-um (n = 21) o placebo (n = 23) durante otras ocho semanas, seguidas de un período de cuatro semanas sin tratamiento. Los gatos se mantuvieron en el estudio hasta que hubo una recaída o hasta el final del periodo de evaluación, lo que ocurriese primero. El resultado fundamental fue el tiempo hasta la recaída. Resultados secundarios fueron la escala análoga visual (pVAS) de prurito, el valor de dermatitis alérgica felina (SCORFAD) y el valor de evaluación global (GAS) del propietario.
Resultados – el tiempo medio de recaída fue de 40,5 días (± 7,8 SE) en gatos tratados con PEA-um (n = 13) y 22,2 días (± 3,7 SE) para el placebo (n = 12; *P* = 0,04). En el día 28, la gravedad del prurito fue menor en los gatos tratados con PEA-um en comparación con el placebo (*P* = 0,03). El empeoramiento medio del prurito en el último día del estudio fue menor en el grupo PEA-um en comparación con el placebo (*P* = 0,04), mientras que el SCORFAD no fue diferente entre los grupos. El GAS promedio del propietario en el último día del estudio fue mejor en el PEA-um que en el grupo tratado con placebo (*P* = 0,05).
Conclusión e importancia clínica – la palmitoiletanolamida ultramicronizada podría representar una opción eficaz y segura para retrasar la recaída en gatos con NFHD.

Zusammenfassung
Hintergrund – Bei Katzen ist die nicht durch Flöhe ausgelöste Hypersensibilitätsdermatitis (NFHD) eine häufige Ursache für zu viel Putzen, Kratzen und für Hautveränderungen. Oft ist eine multimodale Therapie nötig.
Hypothese/Ziele – Eine Untersuchung der Wirksamkeit von ultramikronisiertem Palmitoylethanolamid (PEA-um) um eine durch Methylprednisolon-induzierte Remission bei NFHD Katzen aufrecht zu erhalten.
Tiere – Siebenundfünfzig NFHD Katzen mit nicht saisonalem Juckreiz wurden ursprünglich in die Studie aufgenommen, von denen 25 alle nötigen Studienvoraussetzungen erfüllten, um für die Analyse infrage zu kommen.
Methoden – Die Katzen wurden zufällig eingeteilt, um PEA-um (15 mg/kg *per os*, einmal täglich; n = 29) oder Placebo (n = 28) während eines 28 Tage dauernden graduellen Ausschleichens von Methylprednisolon zu erhalten. Katzen, die gut auf Methylprednisolon ansprachen, bekamen dann PEA-um alleine (n = 21) oder Placebo (n = 23) für weitere acht Wochen, gefolgt von einer vier Wochen dauernden Periode ohne Behandlung. Die Katzen blieben bis zu einem Rückfall oder bis zum Ende in der Studie, je nachdem was zuerst auftrat. Das primäre Ergebnis war die Zeit bis zu einem Rückfall. Das sekundäre Ergebnis umfasste Pruritus Visual Analog Scale (pVAS), SCORing Feline Allergic Dermatitis scale (SCORFAD) und BesitzerInnen Global Assessment Score (GAS).
Ergebnisse – Die durchschnittliche Zeit bis zum Rückfall betrug 40,5 Tage (± 7,8 SE) bei PEA-um behandelten Katzen und 22,2 Tage (± 3,7 SE) bei Plazebo (n = 12; *P* = 0,04). Am Tag 28 war der Schweregrad des Pruritus bei den mit PEA-um behandelten Katzen im Vergleich zu Plazebo behandelten niedriger (*P* =

0,03). Die durchschnittliche Verschlechterung des Pruritus am letzten Studientag war in der PEA-um Gruppe im Vergleich zur Plazebo-Gruppe niedriger (*P* = 0,04), während die SCORFAD zwischen den Gruppen keinen Unterschied aufwies. Die durchschnittliche BesitzerInnen GAS waren am letzten Studientag in der PEA-um Gruppe besser als in der mit Plazebo-behandelten Gruppe (*P* = 0,05).
Schlussfolgerungen und klinische Bedeutung – Ultramikronisiertes Palmitoylethanolamid könnte eine wirksame und sichere Option darstellen, um einen Rückfall bei NFHD Katzen hinauszuzögern.

要約
背景 – 猫非ノミ過敏性皮膚炎(NFHD)は、過剰グルーミング、引っ掻きおよび皮膚病変を頻繁に引き起こす原因の一つである。マルチモーダルな治療がしばしば必要である。
仮説/目的 – 本研究の目的は、NFHD猫のメチルプレドニゾロン誘発寛解維持における超微粉化パルミトイルエタノールアミド(PEA-um)の有効性を検討することである。
動物 – 最初に非季節性掻痒症の57頭のNFHD猫を登録し、そのうち25頭が解析の対象となるためにすべての研究要件を満たした。
方法 – 28日間の漸減メチルプレドニゾロン投与の加療を受ける一方で、猫をランダムにPEA-um投与群(15 mg / kg /経口、1日1回; n = 29)またはプラセボ投与群(n = 28)に割り当てた。次にメチルプレドニゾロンに良好に反応した猫に、さらに8週間PEA-um(n = 21)またはプラセボ(n = 23)のみを投与し、その後4週間無治療期間を設けた。猫は、再発または研究終了のどちらか早い方まで研究を維持した。主な成果は再発までの時間であった。二次的な成果は、掻痒性視覚アナログスケール(pVAS)、SCORing猫アレルギー性皮膚炎スケール(SCORFAD)、および所有者の総合評価スコア(GAS)であった。
結果 – PEA-um投与群猫(n = 13)における平均再発期間は40.5日(±7.8 SE)、プラセボ群では22.2日(±3.7 SE)であった(n = 12; P = 0.04)。 28日目に、掻痒の重症度は、プラセボ群と比較してPEAum投与群猫で低かった(P = 0.03)。最終試験日における掻痒の平均悪化は、プラセボ群と比較してPEA-um群でより低かった(P = 0.04)が、SCORFADにおいては群間で差はなかった。最終試験日における平均所有者GASは、プラセボ群よりもPEAで優れていた(P = 0.05)。
結論と臨床的重要性 – 超微粉化パルミトイルエタノールアミドは、NFHD猫の再発を遅延させる効果的で安全な選択肢を表す可能性がある。

摘要
背景 — 猫非跳蚤过敏性皮炎(NFHD)引起频繁的过度理毛、抓挠和皮肤病变。通常需要多模式治疗。
假设/目的 — 对持续给予甲基强的松龙才能缓解的NFHD猫,研究超微化十六酰胺乙醇(PEA-um)的功效。
动物 — 研究最初征集的具有非季节性瘙痒症的57只NFHD猫,其中仅有25只完成了所有研究要求,符合分析条件。
方法 — 将猫随机分配为PEA-um组(15mg / kg,口服,每日一次; n = 29)和安慰剂组(n = 28),同时将甲基强的松龙在28天内逐渐减至停药。对甲基强的松龙有良好反应的猫在接下来的8周内,仅给予PEA-um(n = 21)或安慰剂(n = 23),然后经历4周的无治疗期。直至猫出现复发或研究结束前一直观察,只记录先出现的情况。主要结果是复发的时间;次要结果是瘙痒视觉模拟量表(pVAS)、猫过敏性皮炎评分(SCORFAD)和主人整体评分(GAS)。
结果 — PEA-um治疗的猫,平均复发时间为40.5天(±7.8 SE)(n = 13);安慰剂组的复发时间为22.2天(±3.7 SE)(n = 12; P = 0.04)。在第28天,与安慰剂相比,PEA-um治疗的猫瘙痒严重程度较低(P = 0.03)。 与安慰剂组相比,PEA-um组最终研究日瘙痒的平均加重程度较低(P = 0.04),而SCORFAD组间没有差异。 最终研究日的平均主人GAS,PEA-um组要优于安慰剂治疗组(P = 0.05)。
结论和临床价值 — 超微化十六酰胺乙醇可能是一种延缓NFHD猫复发的有效、安全的选择。

Resumo
Contexto – A dermatite por hipersensibilidade não responsiva a pulgas (NFHD) é uma causa frequente de toilete em excesso, prurido e lesões de pele. Geralmente, a terapia multimodal é necessária.
Hipótese/Objetivos – Investigar a eficácia da palmitoetanolamida ultramicronizada (PEA-um) na manutenção da remissão clínica induzida pela metilprednisolona.
Animais – Cinquenta e sete gatos NFHD com prurido não sazonal foram incluídos originalmente. Vinte e cinco animais completaram todos os requisitos do estudo para serem elegíveis para a análise.
Métodos – Os gatos foram divididos aleatoriamente em PEA-um (15 mg/kg por via oral, uma vez ao dia; n =29) ou placebo (n = 28) enquanto recebiam um curso de 28 dias metilprednisolona em redução gradual de dose. Os gatos que responderam favoravelmente à metilprednisolona foram então submetidos à administração somente de PEA-um (n = 21) ou placebo (n = 23) por mais oito semanas, seguido por um período sem tratamento com duração de quatro semanas. Os gatos foram mantidos no estudo até recidiva ou final do estudo, o que viesse primeiro. O resultado primário avaliado foi o tempo até a recidiva. Os resultados secundários avaliados foram a escala visual analógica de prurido (pVAS), a escala de classificação de dermatite alérgica felina [*Feline Allergic Dermatitis scale* (SCORFAD)] e o escore de avaliação global pelos proprietários (GAS).
Resultados – O tempo médio de recidiva foi de 40,5 dias (±7,8 EP) nos gatos tratados com PEA-um (n = 13) e 22,2 dias (±3,7 EP) para o placebo (n = 12; *P* = 0,04). No Dia 28, a gravidade do prurido foi menor nos

gatos tratados com PEA-um comparado ao placebo ($P = 0,03$). A média de piora do prurido no dia do final do estudo foi menor no grupo PEA-um comparado ao placebo ($P = 0,04$), enquanto o SCORFAD não apresentou diferença entre os dois grupos. A média do GAS no dia do final do estudo foi melhor no grupo PEA-um que no grupo tratado com placebo ($P = 0.05$).

Conclusão e importância clínica – A palmitoetanolamida ultramicronizada pode representar uma opção de tratamento eficaz e segura de espaçar as recidivas de NFHD em gatos.