Cortotic®

CORTICOSTEROID TREATMENT

ANTIBIOTIC FREE

PROVEN EFFICACY

ANTIFUNGAL FREE

TWIST YOUR VIEW ON OTITIS TREATMENT*

FIRST LINE **WITHOUT AN ANTIMICROBIAL****

A breakthrough, more targeted treatment that delivers proven results in otitis externa without the need for an antibiotic or antifungal.

FOR GOOD HEALTH NOW, **AND IN THE FUTURE.**

Shaping the future of animal health

Virbac

Cortotic® ear spray solution for dogs contains hydrocortisone aceponate 0.584 mg/ml. Target species: Dogs. Indications for use: for the treatment of acute erythemato-ceruminous otitis externa. Contraindications: Do not use in cases of hypersensitivity to the active substance, to other corticosteroids or to any of the excipients. Do not use in animals with perforated tympanic membrane. Do not use in cases of ulcerative lesions. Special warnings: Bacterial and fungal otitis is often secondary in nature. The underlying dermatological condition should be identified and treated. In cases of parasitic otitis, an appropriate acaricidal treatment should be implemented. The presence of foreign bodies, tumors, and any other unusual cause of otitis should be ruled out. In the clinical field trials, only dogs were included diagnosed with otitis externa with the presence of bacterial and/or yeast overgrowth. It was demonstrated that the veterinary medicinal product was non-inferior in treating acute otitis compared to a topic fixed-combination product containing a corticosteroid, an antibiotic and an antimycotic as active substances. A secondary reduction of bacterial and yeast overgrowth was demonstrated and a concomitant treatment with an antimicrobial was unnecessary. The product is thus recommended as a first line treatment of acute erythemato-ceruminous otitis externa. Detailed information (SPC) on this veterinary medicinal product is available on the HPRA (Health Products Regulatory Authority) website https://www.hpra.ie. Use medicines responsibly. Cortotic® may not be available in all countries. Registration conditions may vary across different countries and regions, please check the registered SPC in your respective country.

* For the treatment of acute erythemato-ceruminous otitis externa.
**A secondary reduction of bacterial and yeast overgrowth was demonstrated and a concomitant treatment with an antimicrobial was unnecessary. The product is thus recommended as a first line treatment.

Received: 21 September 2022 | Accepted: 6 July 2023

DOI: 10.1111/vde.13193

Veterinary Dermatology

ORIGINAL ARTICLE

A randomised, double-blinded, controlled trial to determine the efficacy of combined therapy of oclacitinib and marine oil extract PCSO-524 in dogs with atopic dermatitis

Takeo Nishiyama[1] | **Masashi Kusakabe**[1] | **Ichiro Imanishi**[2] | **Tadashi Hisano**[2] | **Teruyasu Fukamachi**[2] | **Norihito Taguchi**[3] | **Keita Iyori**[3] | **Yun-Hsia Hsiao**[3]

[1]Aggie Animal Clinic, Matsudo, Chiba, Japan

[2]Smile Animal Hospital, Funabashi, Chiba, Japan

[3]Vet Derm Tokyo, Dermatological and Laboratory Service for Animals, Fujisawa, Japan

Correspondence
Yun-Hsia Hsiao, Vet Derm Tokyo, Dermatological and Laboratory Service for Animals, 910 Shobusawa, Fujisawa, Kanagawa 252-0823, Japan.
Email: peacha1981@gmail.com

Funding information
V and P Co.

Abstract

Background: Polyunsaturated fatty acids (PUFA) can be beneficial in the management of canine atopic dermatitis (cAD). A commercial product PCSO-524 containing PUFA has demonstrated anti-inflammatory effects in dogs.
Hypothesis/Objectives: To evaluate the efficacy of PCSO-524, in combination with oclacitinib in dogs with cAD.
Animals: Seventeen client-owned dogs with cAD.
Materials and Methods: A randomised, double-blinded, controlled trial. All dogs were treated with oclacitinib (0.4–0.6 mg/kg) twice a day for 14 days, then once a day until Day (D)42. They were randomly divided into two groups: PCSO-524 (n=9) and sunflower oil (n=8). Clinical status was assessed by Canine Atopic Dermatitis Extent and Severity Index, 4th iteration (CADESI-04) and pruritus Visual Analog Scale (pVAS) at baseline (D0), D14, D28 and D42. Trans epidermal water loss (TEWL) was measured at the same time points.
Results: CADESI scores decreased significantly after treatment and there was a significant difference between the PCSO-524 and the control group at D28 (p=0.04) and D42 (p=0.03). The PCSO-524 group also demonstrated a significantly decreased pVAS on D28 and D42 (p<0.001 and p<0.001) compared to D0, while significant differences were observed in the control group at D14 and D28 (p<0.01 and p=0.04) and not at D42 (p=0.12). The mean TEWL showed a significant decrease at D28 and D42 in the PCSO-524 group, compared to the control group (p=0.002 and p<0.001).
Conclusions and Clinical Relevance: The combination of PCSO-524 and oclacitinib may help to alleviate the rebound effect that occurs when tapering down the dosage of oclacitinib, as compared to using oclacitinib alone for the management of cAD.

KEYWORDS
atopic dermatitis, essential fatty acids, oclacitinib, PCSO-524, rebound effect

INTRODUCTION

The pathogenesis of canine atopic dermatitis (cAD) is complex and multifactorial, and usually requires lifelong medical care in order to maintain an acceptable quality of life.[1] During the past decade, a number of proinflammatory and pruritogenic cytokines have been identified as targets for therapy of cAD. However, even with the advent of new-generation medications, such as oclacitinib and lokivetmab, which have good efficacy and a relatively low risk of adverse reactions, multimodal therapeutic strategies are recommended for management of this disease as reviewed in published treatment guidelines.[2,3]

Polyunsaturated fatty acids (PUFAs) appear to have a synergistic effect when used in combination with

antihistamines, corticosteroids or ciclosporin, allowing for improved control of clinical signs or dose reduction of medication.[4] PCSO-524 (Antinol; V and P Co., Ltd) is a patented marine oil extract from the New Zealand green-lipped mussel. The mixture is composed of several types of lipids, including sterol esters, triglycerides, free fatty acids, free sterols and polar lipids. It contains up to 91 fatty acids, with DHA and EPA being the most abundant types of omega-3 polyunsaturated fatty acids.[5] In addition, furan fatty acids (containing a furan ring) in PCSO-524 are considered to possess potent anti-inflammatory properties via the inhibition of both the cyclooxygenase-2 and 5-lipooxygenase pathways, which metabolise arachidonic acid into pro-inflammatory prostanoids and leukotrienes.[6,7] Anecdotal feedbacks from pet owners suggested that PCSO-524 might alleviate the clinical signs of cAD, although the product was developed as an anti-inflammatory for canine osteoarthritis.[8] To the best of the authors' knowledge, there are no published data to evaluate the clinical efficacy of PCSO-524 in dogs with cAD. We hypothesised that combining PCSO-524 with oclacitinib would provide a synergistic effect, particularly when reducing the dosage of oclacitinib in dogs with cAD.

MATERIALS AND METHODS

Animals and diagnostic procedures

The study was conducted in compliance with the Procedures of Good Clinical Practice guidelines issued by the Japanese Ministry of Health, Labour and Welfare. Owners' written consent for their dogs to participate was obtained before the study.

Client-owned dogs with chronic pruritus were recruited in two veterinary facilities between September 2019 and January 2020. The diagnosis of cAD was fulfilled with the clinical criteria proposed by Favrot et al. and followed by compatible history, and other pruritic dermatoses were ruled out based on the standard guidelines.[9,10] Screening examinations consisted of Wood's lamp examination, multiple trichograms and skin scrapings to rule out ectoparasites and cytological evaluation to screen for microbial infections; these were identified by intracellular bacteria based on multiple cytological examinations. Ruling out Malassezia overgrwoth was done in the same manner. Exclusion criteria were systemic and dermatological diseases other than AD. Routine isoxazoline ectoparasiticide prophylaxis was administered during the study. An elimination diet trial was performed on all dogs enrolled in the study and patients that responded either partially or completely after eight weeks of the trial were excluded. Before inclusion, anti-inflammatory and antipruritic medications, such as glucocorticoids (oral or topical), ciclosporin and antihistamines were discontinued for at least two weeks. Dogs treated with long-acting glucocorticoids were excluded. In addition, all topical medications were withdrawn for the same period of time and also prohibited during the whole study. The dogs were continued on their regular diet throughout the study.

Treatment allocation and study protocol

Each dog was randomly assigned to one of two groups using a computer-generated randomisation table. Dogs either received oclacitinib combined with PCSO-524 or were administered oclacitinib combined with the control, sunflower oil capsules. Each PCSO-524 capsule contained a proprietary mix of PCSO-524 (50 mg), olive oil (100 mg) and vitamin E (D-alpha-tocepherol; 0.225 mg). The control capsules contained sunflower oil (139.5 mg/capsule), water and glycerin. The capsules in the PCSO-524 and control groups both contained granules of the same colour and size, so that the owners and investigators were unable to identity the product. Dogs were assessed on the day of enrolment, which was classified as Day (D)0, and then on D14, D28 and D42 by the same veterinary surgeon. All patients received oclacitinib at an initial dose of 0.4–0.6 mg/kg twice daily for 14 days, followed by once daily until D42. Concurrently, dogs in both the PCSO-524 and sunflower oil groups were given capsules twice a day for the first two weeks and once a day thereafter until D42, with the dosage determined based on their body weight (one capsule per 10 kg). Clinical evaluation and pruritus were determined by Canine Atopic Dermatitis Extent and Severity Index, 4th iteration4 (CADESI-04) and a validated owner-assessed pVAS at each visit.[4] Moreover, trans epidermal water loss (TEWL) was measured by a closed chamber device (VAPOSCAN; Asahi-Techno Co. Ltd) at D0 and each time point. Dogs were allowed to acclimatise to the examining area for 30 min before the TEWL measurement. Measurements were made on the inguinal region in a controlled environment (temperature range 20–25°C and humidity range 50%–70%) and repeated three times at each site. The mean of six measurements was used as a representative value. However, if the variation between three measurements exceeded 15%, the results were deemed unreliable and the measurement had to be redone. Adverse events were reported by the owner and if any additional medical treatment was needed, the dog would be withdrawn from the study.

Statistical analysis

All statistical analyses were calculated based on STATVIEW software v5.0 (HULINKS, Inc.). For all statistical analysis, the significant level was set at 5% ($p \leq 0.05$) for the adjusted p-value. The pVAS, CADESI-04 and TEWL of two groups before and after treatment were analysed by a paired t-test, and intergroup differences were analysed with Students t-test.

RESULTS

A total of 17 atopic dogs were recruited in the present study. Group assignment, breed, sex, age, weight and assessment of clinical changes are summarised in Table 1. All dogs completed the study and no adverse events over the course of the study were reported by

TABLE 1 Signalment and clinical scores of the 17 dogs included in the present study.

Group	Age (month)	Body weight (kg)	Breed	Sex	Clinical score				Pruritus score				Trans epidermal water loss (g/m^2/h)			
					D0	D14	D28	D42	D0	D14	D28	D42	D0	D14	D28	D42
PCSO-524	177	3.8	Papillon	FS	43	10	10	8	4	0	0	0	8.2	5.4	4.2	4
PCSO-524	106	6.2	Miniature Dachshund	MC	49	46	36	31	6	3	1	2	16.4	6.7	6	6
PCSO-524	76	8.3	French bulldog	FS	65	14	12	12	7	1	1	1	10.6	4.1	2.3	2.1
PCSO-524	124	4.2	Toy poodle	FS	44	12	8	8	6	1	1	2	8.5	3.1	2.5	2.6
PCSO-524	53	5.4	Shiba inu	MC	38	16	10	8	6	1	0	0	12.1	4.2	2.3	1.8
PCSO-524	104	2.5	Chihuahua	FS	40	18	6	2	7	1	0	0	18.2	10.2	4.8	3.6
PCSO-524	76	7.5	French bulldog	FS	41	13	10	8	5	2	1	1	11.1	4.2	3.7	2.4
PCSO-524	28	12.4	Miniature bulldog	FS	34	13	13	9	7	1	0	0	17.5	7.8	9.5	5.4
PCSO-524	161	7.8	Shiba inu	FS	91	78	37	37	4	1	1	1	21	8.6	6.6	5.7
Placebo	67	3.5	Toy poodle	FS	37	18	22	18	5	1	2	3	10.4	8.7	6.2	6.9
Placebo	96	5.1	Bichon frise	MC	42	24	38	40	5	1	3	4	7.2	5.6	8.4	8.8
Placebo	96	7.6	Shiba inu	FS	86	59	43	27	7	4	4	4	13.1	5.8	6	6.4
Placebo	185	3.9	Toy poodle	FS	41	33	27	26	5	1	0	0	9.1	9.3	9.4	7.4
Placebo	24	3	Chihuahua	MC	14	10	16	10	6	1	7	7	7.9	8	8.7	8.4
Placebo	174	6.8	Miniature Dachshund	MC	26	16	20	22	5	2	3	3	8.6	7.8	8.2	9.4
Placebo	164	4.4	Shiba inu	MC	18	16	22	28	4	4	4	5	9.6	6.2	8.8	9.2
Placebo	76	8.5	French bulldog	FS	52	26	38	46	6	3	5	6	12.4	10.8	11.4	13.6

Abbreviations: D, Day; FS, female spayed; MC, male castrated.

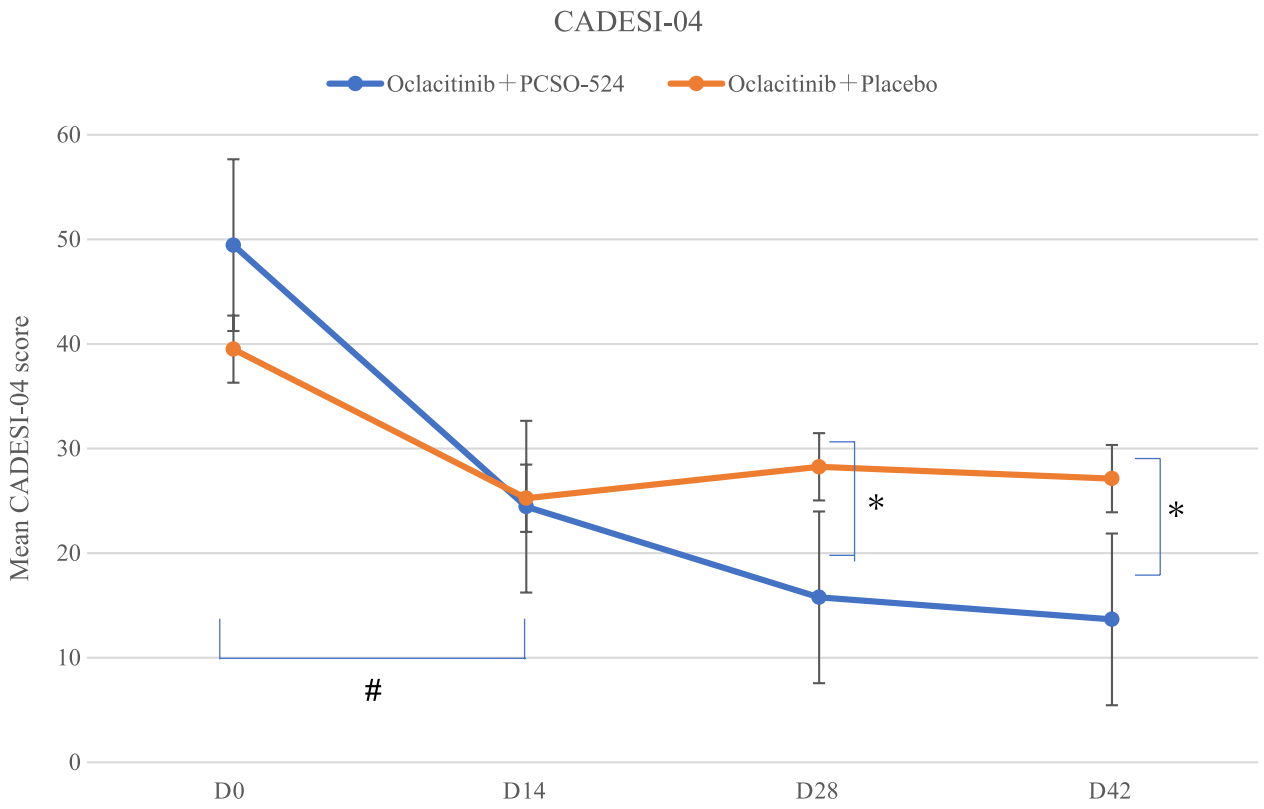

FIGURE 1 Changes in pruritus Visual Analog Scale (pVAS) after the oclacitinib combined with PCSO-524 or control. Results show the significant decrease at Day (D)28 and D42 in the PCSO-524 group.

the owners. Nine dogs were in the PCSO-524 group and eight dogs were in the control group.

CADESI-04

Means±standard deviation (SD) of the CADESI-04 for both groups across all time points are presented in Figure 1. At D14, both groups showed a significant decrease compared to the baseline (both $p<0.001$). The mean CADESI-04 reduced from 49.4±17.9 to 24.4±22.8 in the PCSO-524 group, and from 39.5±21.2 to 14±3 in the control group. No significant differences were found between the PCSO-524 and control groups at D0 and D14 ($p=0.33$ and $p=0.93$). However, there was a significant improvement in the PCSO-524 group at D28 and D42 (15.7±11.9 and 13.7±11.9, respectively; $p=0.004$ and $p=0.03$) compared to the control group (28.2±9.3 and 27.1±10.7). Additionally, the PCSO-524 group exhibited a significant decrease over time when compared to D0 ($p=0.003$, $p<0.001$ and $p<0.001$ for D14, D28 and D42, respectively).

pVAS

The mean pVAS and SD for two groups is illustrated in Figure 2. Both groups showed a significantly decline in pVAS score at D14 compared to the baseline while on twice-daily oclacitinib ($p<0.001$ and $p<0.001$). In the control group, mean pVAS reduced from 5.4±0.8 at D0 to 3.5±1.9 at D28 and 4.0±2.0 at D42, compared to the baseline ($p=0.04$ and $p=0.12$). In the PCSO-524 group, the mean pVAS was 5.8±1.2 at D0 and reduced to 0.5±0.5 at D28 and 0.7±0.7 at D42, both of which were statistically significant compared to D0 ($p<0.001$ and $p<0.001$). There was a significant different in pVAS between the two groups at D28 and D42 ($p<0.001$ and $p<0.001$) (Figure 2).

TEWL

Changes over time in TEWL with mean and SD are shown in Figure 3. There was a significant difference in the TEWL between the PCSO-524 group and the control at D0 ($p=0.04$). In the control group, there was no statistical significance in mean values when D0 was compared with D14, D28 and D42 ($p=0.06$, $p=0.17$ and $p=0.31$). However, a consistent reduction in TEWL was observed in the PCSO-524 group, reducing from 13.7±4.7 at D0 to 6.0±2.4 at D14, 4.6±2.4 at D28 and 3.7±1.6 at D42 as compared to D0 (all $p<0.001$).

DISCUSSION

This randomised, double-blinded, controlled clinical trial demonstrates a significant improvement in pruritus, clinical signs (as assessed by CADESI-04) and TEWL in dogs treated with oclacitinib and PCSO-524 concurrently when compared with the control group of oclacitinib and sunflower oil. Furthermore, the outcome suggests that PCSO-524 combined with

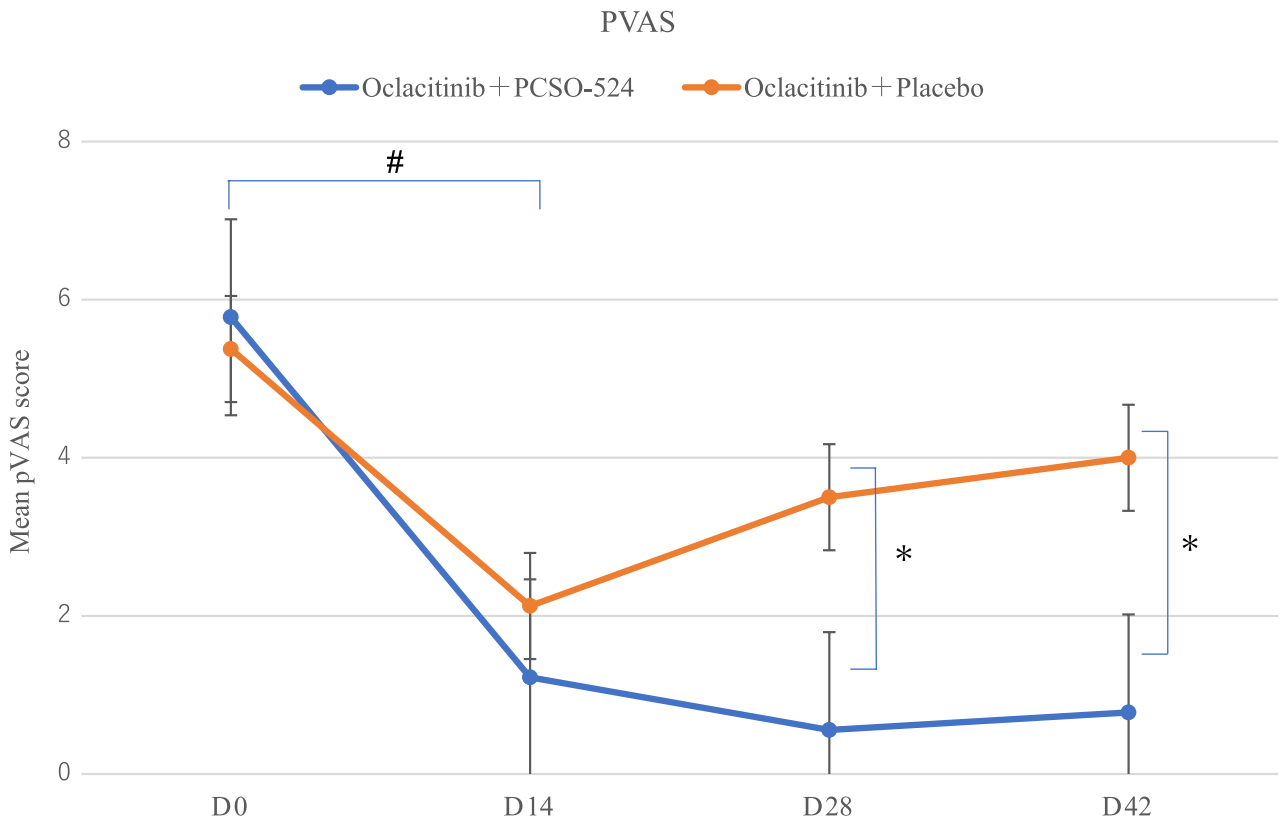

FIGURE 2 Effects of PCSO-524 on Canine Atopic Dermatitis Extent and Severity Index, 4th iteration (CADESI-04) in the PCSO-524 and placebo groups. The PCSO-524 group demonstrated significant improvement compared to the control group at Day (D)28 and D42.

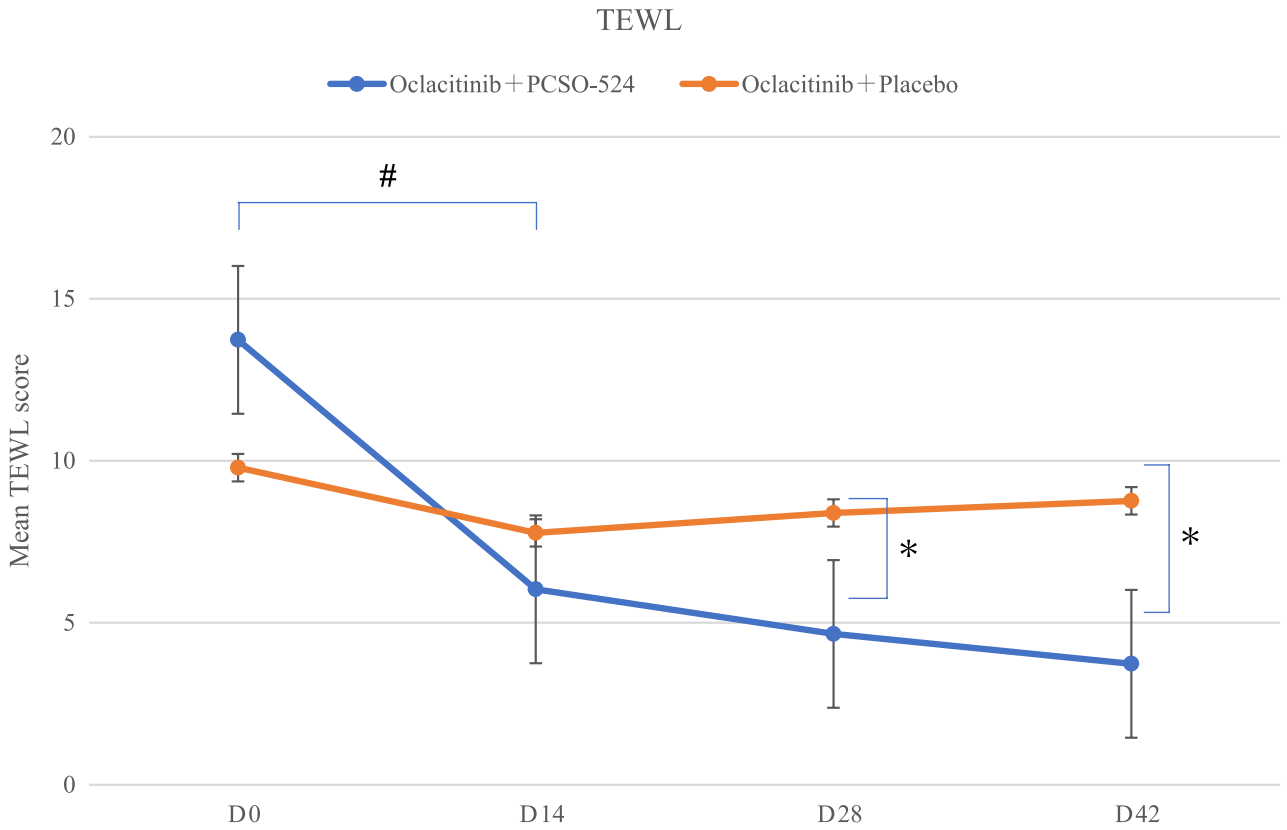

FIGURE 3 Changes in the trans epidermal water loss (TEWL) of the control and PCSO-524 groups in the clinical trial. No significant effects were observed in the control group, while the PCSO-524 group showed steady and significant improvement.

oclacitinib may compensate for a potential rebound in pruritus when oclacitinib was reduced to once daily dosing after D14.

Oclacitinib is an immunomodulatory drug that blocks the pro-inflammatory and pruritogenic cytokines through the Janus kinase (JAK) signalling pathway. The

'rebound phenomenon' of pruritus was reported in clinical cases when the dose was tapered from twice to once daily.[11] Recently, a clinical study of client owned dogs with cAD demonstrated that 33 of 53 (73%) were unable to taper the dose of oclacitinib from twice daily to once daily without the dogs experiencing an increase in pruritus.[12] To manage the pruritus effectively, prolonged twice-daily therapy was recommended, which is associated with an extra burden of routine blood tests and an increased risk of adverse effects. In our study, we also observed a rebound in pruritus at D14 after reducing to once daily oclacitinib in the control group; however, the dogs in the PCSO-524 group remained well controlled after 14 days. In the current study, the CADESI-04 scores of the PCSO-524 group at D28 and D42 did not show a significant difference ($p=0.28$ and $p=0.18$) compared to D14, yet they were significantly different when compared to the control group at D28 and D42 ($p=0.04$ and $p=0.03$). In addition, only one dog achieved pVAS <2 (a normal score) in the control group at D42, while all dogs showed pVAS <2 in the PCSO-524 group at D28 and D42. Despite being a relatively short-term study compared to other clinical studies on fatty acids, the current study aimed to observe the efficacy of synergistic therapy of PCSO-524 and oclacitinib. A review paper has reviewed 25 studies that evaluated the efficacy of various commercial fatty acid supplements containing omega-3 and/or omega-6 FA for treating cAD.[13] The studies were categorised based on the duration of treatment, with short-term studies lasting 2–8 weeks and long-term studies lasting 8–16 weeks. During short-term observation, the focus is primarily on changes in pruritus and clinical improvement. By contrast, long-term observation focuses primarily on the medical-sparing effect or the use of fatty acid supplements as a sole therapy. Under these conditions, a 42 day trial period would be sufficient for observing the effect of combined therapy with PCSO-524 and oclacitinib. In 2019, a blinded, placebo-controlled study recruited a group of dogs with spontaneous cAD and fed a diet containing polyphenols, antioxidants and omega-3 fatty acid alongside with oclacitinib (0.4–0.6 mg/kg twice daily for 14 days then tapered to once a day) for a 60 day trial.[14] The study found that the combination of fatty acids and oclacitinib led to a significant improvement in clinical scores, specifically the CADESI-04 and pruritus scores, compared to the placebo group at both D30 and D60.[14] These findings were similar to ours and suggest that fatty acid combined with oclacitinib can enhance the anti-inflammatory effect and benefit clinical scores after reducing the dosage. The anti-inflammatory efficacy of PCSO-524 can be attributed to the supplement's functional ingredient furan fatty acids.[6] Furan fatty acids have been examined in various assay systems for anti-inflammatory activity, including in vitro and in vivo studies, modifying the leukotriene and prostaglandin production in the lipoxygenase and cyclooxygenase pathways.[8]

TEWL is one physiological parameter to evaluate skin barrier function in dogs, yet its usefulness has remained controversial as a result of the lack of a consistent methodology.[15,16] Several studies have examined TEWL as a means of evaluating treatment efficacy in lokivetmab, ciclosporin and hydrocortisone aceponate (HCA) spray,[17–19] yet comparing the results across different studies can be difficult. In the study by Marsella et al., eight dogs were randomly assigned to receive either an oclacitinib or control for four weeks and followed by a wash-out period of four weeks, and then crossed-over to the other group. The study recruited a colony of atopic beagle dogs that were exposed to allergens in a controlled manner, in an attempt to replicate the natural occurring AD in dogs. Interestingly, the use of oclacitinib led to a significant increase in TEWL in the inguinal area, which is different from our findings as we did not observe significant changes in control group.[16] It could be challenging to interpret the differences as both studies have a limited sample size, various level of inflammation and individual physiological changes. Despite the limitations in clinical studies, an animal model combining in vivo and in vitro methods could offer more comprehensive insights into this phenomenon by biomolecular evidence. A microarray analysis using a mouse/human skin model revealed that the inflammatory cytokines interleukin (IL)-4/IL-13 may impair skin barrier function by downregulating epidermal differentiation via the JAK-signal transducers and activators of transcription (STAT) signalling pathway.[20] This suggests that oclacitinib, as a JAK inhibitor, may have the potential to improve abnormal keratinocyte differentiation by reversing the gene expression alteration observed in AD lesions. Despite the proposed hypothesis, it is important to remember that TEWL is merely one physiological parameter and should not be overemphasised in its role in skin barrier function.

Sunflower oil is not considered a significant source of omega-3 fatty acid, yet it is a good source of omega-6 fatty acid, particularly linoleic acid which is an important component of the stratum corneum in dogs. In a previous study involving client-owned dogs, it was demonstrated that sunflower oil had no impact on TEWL and the activity of various chemokines and cytokines during a four week wash-in period.[21] As a result, we employed sunflower oil as the control in our study. Based on current evidence, the inclusion of vitamine E in the capsule has shown no significant impact on skin barrier function. Vitamine E is not suggested as a treatment option for cAD. Therefore, we do not regard it as an actvie ingreident in this product.

The limitations of this study are the small number of dogs, the lack of dietary fatty acid standardisation and its relatively short duration. In addition, the TEWL did not shown a normal distribution at the inclusion at D0. Despite the improvement seen in the PCSO-524 group, a 12 week study period with controlled diet might provide a more precise conclusion.

In conclusion, based on the results from this study on the 17 atopic dogs examined, we postulate that the anti-inflammatory effects of PCSO-524 compensated for the rebound effect which is often seen when oclacitinib is reduced to once daily dosing after D14. PCSO-524 supplementation also reduced the TEWL and this finding warrants further investigation.

AUTHOR CONTRIBUTIONS

Takeo Nishiyama: Writing—original draft; project administration; software; resources; investigation; data curation; formal analysis. **Masashi Kusakabe:** Project administration. **Ichiro Imanishi:** Resources. **Tadashi Hisano:** Project administration. **Teruyasu Fukamachi:** Project administration. **Norihito Taguchi:** Project administration. **Keita Iyori:** Supervision; funding acquisition; methodology. **Yun–Hsia Hsiao:** Writing—review & editing; writing—original draft; validation.

ACKNOWLEDGEMENTS

The authors thank the owners and their canine companions that participated in the clinical trial.

FUNDING INFORMATION

This study was partly financially supported by V and P Co., (https://vetzpetz.jp/pages/company) which also supplied the capsules used in the trial. The funders had no role in study design, data collection and analysis, in writing the manuscript or decision to publish.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Keita Iyori https://orcid.org/0000-0003-1977-4201
Yun-Hsia Hsiao https://orcid.org/0000-0002-9867-7268

REFERENCES

1. Marsella R, De Benedetto A. Atopic dermatitis in animals and people: an update and comparative review. Vet Sci. 2017;4:37–56.
2. Olivry T, DeBoer DJ, Favrot C, Jackson HA, Mueller RS, Nuttall T, et al. Treatment of canine atopic dermatitis: 2010 clinical practice guidelines from the international task force on canine atopic dermatitis. Vet Dermatol. 2010;21:233–48.
3. Olivry T, DeBoer DJ, Favrot C, Jackson HA, Mueller RS, Nuttall T, et al. Treatment of canine atopic dermatitis: 2015 updated guidelines from the international committee on allergic diseases of animals (ICADA). BMC Vet Res. 2015;11:210–25.
4. Müller MR, Linek M, Löwenstein C, Röthig A, Doucette K, Thorstensen K, et al. Evaluation of cyclosporine-sparing effects of polyunsaturated fatty acids in the treatment of canine atopic dermatitis. Vet J. 2016;210:77–81.
5. Mickleborough TD, Sinex JA, Platt D, Chapman RF, Hirt M. The effects PCSO-524®, a patented marine oil lipid and omega-3 PUFA blend derived from the New Zealand green lipped mussel (Perna canaliculus), on indirect markers of muscle damage and inflammation after muscle damaging exercise in untrained men: a randomized, placebo controlled trial. J Int Soc Sports Nutr. 2015;12:10.
6. Wakimoto T, Kondo H, Nii H, Kimura K, Egami Y, Oka Y, et al. Furan fatty acid as an anti-inflammatory component from the green-lipped mussel *Perna canaliculus*. Proc Natl Acad Sci U S A. 2011;108:17533–37.
7. Whitehouse MW, Macrides TA, Kalafatis N, Betts WH, Haynes DR, Broadbent J. Anti-inflammatory activity of a lipid fraction (lyprinol) from the NZ green-lipped mussel. Inflammopharmacology. 1997;5:237–46.
8. Vijarnsorn M, Kwananocha I, Kashemsant N, Jarudecha T, Lekcharoensuk C, Beale B, et al. The effectiveness of marine based fatty acid compound (PCSO-524) and firocoxib in the treatment of canine osteoarthritis. BMC Vet Res. 2019;15:349–57.
9. Hensel P, Santoro D, Favrot C, Hill P, Griffin C. Canine atopic dermatitis: detailed guidelines for diagnosis and allergen identification. BMC Vet Res. 2015;11:196–209.
10. Favrot C, Steffan J, Seewald W, Picco F. A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. Vet Dermatol. 2010;21:23–31.
11. Fukuyama T, Ganchingco JR, Bäumer W. Demonstration of rebound phenomenon following abrupt withdrawal of the JAK1 inhibitor oclacitinib. Eur J Pharmacol. 2017;794:20–6.
12. Denti D, Caldin M, Ventura L, De Lucia M. Prolonged twice-daily administration of oclacitinib for the control of canine atopic dermatitis: a retrospective study of 53 client-owned atopic dogs. Vet Dermatol. 2022;33:149-e142.
13. van Amersfort K, van der Lee A, Hagen-Plantinga E. Evidence-base for the beneficial effect of nutraceuticals in canine dermatological immune-mediated inflammatory diseases – A literature review. Vet Dermatol. 2023;34:266–83.
14. de Santiago MS, Arribas JLG, Llamas YM, Becvarova I, Meyer H. Randomized, double-blind, placebo-controlled clinical trial measuring the effect of a dietetic food on dermatologic scoring and pruritus in dogs with atopic dermatitis. BMC Vet Res. 2021;17:354.
15. Marsella R, Ahrens K. A pilot study on the effect of oclacitinib on epicutaneous sensitization and transepidermal water loss in a colony of atopic beagle dogs. Vet Dermatol. 2018;29:439-e146.
16. Marsella R, Ahrens K, Wilkes R, Trujillo A, Dorr M. Comparison of various treatment options for canine atopic dermatitis: a blinded, randomized, controlled study in a colony of research atopic beagle dogs. Vet Dermatol. 2020;31:284-e269.
17. Szczepanik M, Wilkołek P, Gołyński M, Sitkowski W, Taszkun I, Toczek W. The influence of treatment with lokivetmab on transepidermal water loss (TEWL) in dogs with spontaneously occurring atopic dermatitis. Vet Dermatol. 2019;30:330-e393.
18. Zając M, Szczepanik M, Wilkołek P, Adamek Ł, Pomorski Z. The influence of non-specific anti-pruritus treatment with cyclosporine a on transepidermal water loss (TEWL) in natural atopic dermatitis in dogs. Pol J Vet Sci. 2015;18:415–24.
19. Nam EH, Park SH, Jung JY, Han SH, Youn HY, Chae JS, et al. Evaluation of the effect of a 0.0584% hydrocortisone aceponate spray on clinical signs and skin barrier function in dogs with atopic dermatitis. J Vet Sci. 2012;13:187–91.
20. Amano W, Nakajima S, Kunugi H, Numata Y, Kitoh A, Egawa G, et al. The Janus kinase inhibitor JTE-052 improves skin barrier function through suppressing signal transducer and activator of transcription 3 signaling. J Allergy Clin Immunol. 2015;136:667–77.e667.
21. Richards TL, Burron S, Ma DWL, Pearson W, Trevizan L, Minikhiem D, et al. Effects of dietary camelina, flaxseed, and canola oil supplementation on inflammatory and oxidative markers, transepidermal water loss, and coat quality in healthy adult dogs. Front Vet Sci. 2023;10:1085890.

How to cite this article: Nishiyama T, Kusakabe M, Imanishi I, Hisano T, Fukamachi T, Taguchi N, et al. A randomised, double-blinded, controlled trial to determine the efficacy of combined therapy of oclacitinib and marine oil extract PCSO-524 in dogs with atopic dermatitis. Vet Dermatol. 2023;00:1–9. https://doi.org/10.1111/vde.13193

摘要

背景: 多不饱和脂肪酸(PUFA)可用于治疗犬特应性皮炎(cAD)。含有PUFA的商业产品PCSO-524已在犬身上显示出抗炎作用。

假设/目的: 评估PCSO-524联合奥拉替尼治疗犬cAD的疗效。

动物: 17只客户饲养的cAD患犬。

材料和方法: 一项随机、双盲、对照试验。所有犬均接受奥拉替尼(0.4–0.6 mg/kg , 每天两次 , 持续14天 , 然后每天一次 , 直到第42天(D)。他们被随机分为两组。PCSO-524(n=9)和向日葵油(n=8)。在基线(D0)、D14、D28和D42时 , 通过犬特应性皮炎程度和严重程度指数、第4次迭代(CADESI-04)和瘙痒视觉模拟量表(pVAS)评估临床状态。在相同的时间点测量经表皮水分流失(TEWL)。

结果: 治疗后CADESI评分显著下降 , PCSO-524组与对照组在D28(p=0.04)和D42(p=0.03)时有显著差异 , 而对照组在D14和D28时观察到显著差异(p<0.01和p=0.04) , 而在D42时没有(p=0.12)。与对照组相比 , PCSO-524组在D28和D42时的平均TEWL显著降低(p=0.002和p<0.001)。

结论和临床相关性: 与单独使用奥拉替尼治疗cAD相比 , PCSO-524和奥拉替尼的联合用药可能有助于缓解减少奥拉替尼剂量时出现的反弹效应。

Résumé

Contexte: Les acides gras polyinsaturés (AGPI) peuvent être bénéfiques dans le traitement de la dermatite atopique canine (DAC). Un produit commercial, le PCSO-524, contenant des AGPI, démontre des effets anti-inflammatoires chez les chiens.

Hypothèse/objectifs: Évaluer l'efficacité du PCSO-524, en association avec l'oclacitinib, chez les chiens atteints de DAC.

Animaux: Dix-sept chiens appartenant à des clients et souffrant de DAC.

Matériels et méthodes: Essai contrôlé, randomisé, en double aveugle. Tous les chiens sont traités avec de l'oclacitinib (0,4-0,6 mg/kg deux fois par jour pendant 14 jours, puis une fois par jour jusqu'au jour (J)42. Ils sont répartis aléatoirement en deux groupes. PCSO-524 (n=9) et huile de tournesol (n=8). Le score clinique est évalué par le « Canine Atopic Dermatitis Extent and Severity Index, 4éme édition» (CADESI-04) et par l'échelle visuelle analogique du prurit (pVAS) au début de l'étude (J0), à J14, à J28 et à J42. La perte d'eau transépidermique (TEWL) est mesurée aux mêmes moments.

Résultats: Les scores CADESI diminuent de manière significative après le traitement et il y a une différence significative entre le groupe PCSO-524 et le groupe témoin à J28 (p=0,04) et J42 (p=0,03). Le groupe PCSO-524 montre également une diminution significative du pVAS à J28 et J42 (p <0,001 et p <0,001) par rapport à J0, alors que des différences significatives sont observées dans le groupe témoin à J14 et J28 (p <0,01 et p=0,04), mais pas à J42 (p=0,12). Le TEWL moyen diminue significativement à J28 et J42 dans le groupe PCSO-524, par rapport au groupe témoin (p=0,002 et p <0,001).

Conclusions et pertinence clinique: L'association de PCSO-524 et d'oclacitinib peut contribuer à atténuer l'effet rebond qui se produit lors de la réduction progressive de la dose d'oclacitinib, par rapport à l'utilisation de l'oclacitinib seul pour la prise en charge de la DAC.

要約

背景: 多価不飽和脂肪酸(PUFA)は犬アトピー性皮膚炎(cAD)の管理に有益である。PUFAを含む市販製品PCSO-524は、犬において抗炎症効果を示した。

仮説/目的: 本研究の目的は、PCSO-524およびオクラシチニブの併用によるcADに対する有効性を評価することであった。

対象動物: cADを有するオーナー所有犬17頭。

材料と方法: 無作為化二重盲検比較試験を実施した。すべての犬にオクラシチニブ(0.4~0.6mg/kgを1日2回、14日間投与し、その後1日1回、42日目まで投与)を投与した。無作為にPCSO-524(n=9)投与群およびヒマワリ油(n=8)投与群の2群に分けられた。臨床状態は、試験開始0日目、14日目、28日目および42日目において、Canine Atopic Dermatitis Extent and Severity Index, 4th iteration(CADESI-04)および痒みのVisual Analog Scale(pVAS)で評価した。経皮水分蒸散量(TEWL)も同じ時点で測定した。

結果: CADESIスコアは治療後に有意に減少し、28日目(p=0.04)および42日目(p=0.03)においてPCSO-524群および対照群間に有意差が認められた。PCSO-524群はまた、試験開始日と比較して28日目および42日目でpVASの有意な減少を示したが(p<0.001とp<0.001)、対照群では14日目および28日目で有意差が観察された(p<0.01とp=0.04)が、42日目では観察されなかった(p=0.12)。平均TEWLは、PCSO-524群で28日目および42日目において、対照群と比較して有意な減少を示した(p=0.002およびp <0.001)。

結論と臨床的意義: PCSO-524およびオクラシチニブの併用は、cADの管理にオクラシチニブ単独使用した場合と比較して、オクラシチニブの用量を漸減する際に生じるリバウンド効果を軽減するのに役立つ可能性がある。

Resumo

Contexto: Os ácidos graxos poliinsaturados (PUFA) podem ser benéficos no tratamento da dermatite atópica canina (DAC). Um produto comercial PCSO-524 contendo PUFA demonstrou efeito anti-inflamatório em cães.

Hipótese/Objetivos: Avaliar a eficácia do PCSO-524, em combinação com oclacitinib, em cães com DAC.

Animais: Dezessete cães de clientes com DAC.

Materiais e métodos: Um estudo randomizado, duplo-cego e controlado. Todos os cães foram tratados com oclacitinib (0,4–0,6 mg/kg duas vezes ao dia por 14 dias, depois uma vez ao dia até o Dia (D)42. Eles foram divididos aleatoriamente em dois grupos. PCSO-524 (n=9) e óleo de girassol (n=8). A avaliação clínica foi feita utilizando o Índice de Extensão e Gravidade da Dermatite Atópica Canina, 4ª iteração (CADESI-04) e Escala Visual Analógica de prurido (pVAS) no tempo zero (D0), D14, D28 e D42. Mensurou-se a perda de água transepidérmica (TEWL) nos mesmos pontos de tempo.
Resultados: Os escores CADESI diminuíram significativamente após o tratamento e houve uma diferença significativa entre o PCSO-524 e o grupo controle em D28 (p =0,04) e D42 (p=0,03). O grupo PCSO-524 também demonstrou uma pVAS significativamente diminuída em D28 e D42 (p <0,001 e p <0,001) em comparação com D0, enquanto diferenças significativas foram observadas no grupo controle em D14 e D28 (p <0,01 e p =0,04) , e não em D42 (p =0,12). A média TEWL apresentou uma diminuição significativa em D28 e D42 no grupo PCSO-524, em comparação com o grupo controle (p =0,002 e p <0,001).
Conclusões e Relevância Clínica: A combinação de PCSO-524 e oclacitinib pode ajudar a aliviar o efeito rebote que ocorre ao diminuir a dosagem de oclacitinib, em comparação com o uso de oclacitinib em monoterapia para o tratamento da DAC.

RESUMEN

Introducción: Los ácidos grasos poliinsaturados (PUFA) pueden ser beneficiosos en el tratamiento de la dermatitis atópica canina (cAD). Un producto comercial PCSO-524 que contiene PUFA ha demostrado efectos antiinflamatorios en perros.
Hipótesis/Objetivos: Evaluar la eficacia de PCSO-524, en combinación con oclacitinib en perros con cAD.
Animales: Diecisiete perros de propietarios particulares con cAD.
Materiales y métodos: Ensayo controlado, al azar, doble ciego. Todos los perros fueron tratados con oclacitinib (0,4–0,6 mg/kg dos veces al día durante 14 días, luego una vez al día hasta el Día (D)42. Se dividieron al azar en dos grupos. PCSO-524 (n=9) y aceite de girasol (n=8). El estado clínico se evaluó mediante el índice de extensión y gravedad de la dermatitis atópica canina, cuarta revisión (CADESI-04) y la escala análoga visual de prurito (pVAS) al inicio (D0), D14, D28 y D42. La pérdida de agua transepidérmica (TEWL) se midió en los mismos puntos de tiempo.
Resultados: las puntuaciones de CADESI disminuyeron significativamente después del tratamiento y hubo una diferencia significativa entre PCSO-524 y el grupo de control en D28 (p =0,04) y D42 (p =0,03). El grupo PCSO-524 también demostró una pVAS significativamente menor en D28 y D42 (p <0,001 y p <0,001) en comparación con D0, mientras que se observaron diferencias significativas en el grupo de control en D14 y D28 (p <0,01 y p =0,04), y no en D42 (p =0,12). La TEWL media mostró una disminución significativa en D28 y D42 en el grupo PCSO-524, en comparación con el grupo control (p =0,002 y p <0,001).
Conclusiones y relevancia clínica: la combinación de PCSO-524 y oclacitinib puede ayudar a aliviar el efecto rebote que se produce cuando se reduce gradualmente la dosis de oclacitinib, en comparación con el uso de oclacitinib solo para el tratamiento de la cAD.

Zusammenfassung

Hintergrund: Mehrfach ungesättigte Fettsäuren (PUFA) können beim Management der caninen atopischen Dermatitis (cAD) hilfreich sein. Ein kommerzielles Produkt PCSO-524, welches PUFA enthält, hat entzündungshemmende Wirkung bei Hunden bewiesen.
Hypothese/Ziele: Das Ziel war eine Evaluierung der Wirksamkeit von PCSO-524 in Kombination mit Oclacitinib bei Hunden mit cAD.
Tiere: Siebzehn Hunde mit cAD, welche in Privatbesitz waren.
Materialien und Methoden: Es handelt sich um eine randomisierte, doppelblinde kontrollierte Studie. Alle Hunde wurden mit Oclacitinib (0,4-0,6 mg/kg) zweimal täglich 14 Tage lang behandelt, danach einmal täglich bis zum Tag (D) 42. Die Hunde wurden zufällig in zwei Gruppen eingeteilt: PCSO-524 (n=9) und Sonnenblumenöl (n=8). Der klinische Status wurde mittels Canine Atopic Dermatitis Extent and Severity Index, 4te Auflage (CADESI-04) und der Pruritus Visual Analog Scale (pVAS) zum Ausgangspunkt (D0), D14, D28 und D42 erfasst. Der transepidermale Wasserverlust (TEWL) wurde zu diesen Zeitpunkten ebenfalls erfasst.
Ergebnisse: Die CADESI Werte nahmen nach der Behandlung signifikant ab und es bestand ein signifikanter Unterschied zwischen der PCSO-524 und der Kontrollgruppe am D28 (p =0,04) und D42 (p =0,03). Die PCSO-524 Gruppe zeigte außerdem eine signifikant reduzierte pVAS am D28 und D42 (p <0,001 und p <0,001) im Vergleich zu D0, während in der Kontrollgruppe signifikante Unterschiede am D14 und D28 (p <0,01 und p =0,04), aber nicht am D42 (p =0,12) festgestellt wurden. Der durchschnittliche TEWL zeigte am D28 und D42 (p=0,002 und p <0,001) in der PCSO-524 Gruppe im Vergleich zur Kontrollgruppe eine signifikante Reduktion.
Schlussfolgerungen und klinische Relevanz: Die Kombination von PCSO-524 und Oclacitinib könnte im Vergleich zum alleinigen Einsatz von Oclacitinib dabei helfen, den Rebound Effekt, der bei der Reduzierung der Oclacitinib Dosis eintritt, auszugleichen.