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The effect of a spot-on formulation containing polyunsaturated fatty acids and essential oils on dogs with atopic dermatitis

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Abstract

Recent studies have shown that immunological aberrations and epidermal barrier defects could be important in the pathogenesis of canine atopic dermatitis (CAD) and that oral polyunsaturated fatty acids (PUFAs) might influence the epidermal barrier. The aim of this study was to evaluate the effects of a spot-on formulation containing PUFAs and essential oils on pruritus and lesions caused by CAD. Forty-eight privately owned dogs of different breeds, ages and genders diagnosed with atopic dermatitis were included in a randomized, double-blinded, placebo-controlled, multicentre clinical trial. Dogs were treated with a spot-on formulation containing PUFAs and essential oils or placebo on the dorsal neck once weekly for 8 weeks. Before and after the study, CAD extent and severity index-03 (CADESI-03) and pruritus scores were determined by veterinarians and owners, respectively.

There was significantly more improvement in CADESI-03 and pruritus scores in the treatment group than in the placebo group (P=0.011 and P=0.036, respectively). Additionally, more dogs improved by at least 50% in CADESI-03 and pruritus scores in the treatment group than in the placebo group (P=0.008 and P=0.070, respectively). No adverse reactions were observed. The topical preparation containing PUFAs and essential oils was a safe treatment and beneficial in ameliorating the clinical signs of CAD.

Keywords

Atopic dermatitis; Canine; Essential fatty acids; Topical therapy

Introduction

Canine atopic dermatitis (CAD) is a commonly presented disease in veterinary practice (Scott and Paradis, 1990) and is associated with pruritus (Griffin and DeBoer, 2001 and Saridomichelakis et al., 1999) and skin lesions (Favrot et al., 2010 and Griffin and DeBoer, 2001). It is diagnosed by history, clinical signs and the exclusion of differential diagnoses, and clinical diagnostic criteria have been recently introduced (Favrot et al., 2010). In CAD, a hypersensitivity response against environmental or food allergens develops due to a genetic predisposition and could be associated with disturbances in the skin barrier function (Merryman-Simpson et al., 2008, Sandilands et al., 2009 and Wood et al., 2009). Allergens involved in the pathogenesis of non-food-induced CAD include house dust mites, pollens, moulds and insect antigens (Hill and DeBoer, 2001). Allergens can be inhaled or percutaneously absorbed (Marsella et al., 2006 and Olivry and Hill, 2001a).

Symptomatic treatment for CAD includes antihistamines, glucocorticoids, cyclosporin, topical therapy, and polyunsaturated fatty acids (PUFAs), while specific treatment employs allergen-specific immunotherapy (Olivry et al., 2010). PUFAs cannot be synthesized de novo and need to be ingested pre-formed in the diet. They contain one or more double bonds, and are classified as omega-3 and omega-6 fatty acids, depending on the position of the first double bond relative to the carboxy end of the chain. Important omega -3 fatty acids are α-linolenic acid (in linseed oil), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA; in fish oils). Omega-6 fatty acids are linoleic acid (in sunflower or safflower oil), γ-linoleic acid (in evening primrose oil) and dihomo-γ-linoleic acid.

In vitro, PUFAs are reported to have anti-inflammatory (Ziboh and Chapkin, 1988 and Ziboh et al., 2000) and immunomodulating (Stehle et al., 2010) effects. A further possible mechanism of action is improvement of the epidermal barrier function, presumably by changing the composition of epidermal lipids. Oral fatty acid supplementation has been reported to change cutaneous lipids in Beagle dogs (Campbell et al., 1992).

In contrast to many other symptomatic therapies for CAD, oral supplementation with PUFAs rarely causes adverse effects (Mueller et al., 2004 and Olivry et al., 2001b), although diarrhoea might occur with oral supplementation (Scott et al., 1992). Adverse effects of topically administered PUFA therapy have not been reported (Tretter and Mueller, 2011). Concurrent treatment with PUFAs might permit reduction of the dosage of other anti-inflammatory medications, such as glucocorticoids, and further improvement in clinical signs (Bond and Lloyd, 1994, Saevik et al., 2004 and Scott and Miller, 1993).

Studies on the use of oral fatty acid supplementation have been published (Mueller et al., 2004 and Saevik et al., 2004), but reports about the efficacy of topically applied PUFAs or ceramides are rare and describe non-blinded and open trials (Piekutowska et al., 2008 and Tretter and Mueller, 2011). The aim of this study was to evaluate the efficacy of a commercial spot-on containing PUFAs and essential oils on the clinical signs of CAD in a prospective, placebo-controlled, randomised trial.

Materials and methods

The study was approved by the Ethics Committee of the Centre for Clinical Veterinary Medicine/Ludwig Maximilian University Munich (Approval number 03-051012). Prior to enrolment, dog owners gave their written consent (Appendix A: Supplementary Material).

Study design and study objects

This was a randomized, double-blinded, placebo-controlled multicentre study. Three dermatology referral practices in Germany (Centre for Clinical Veterinary Medicine, Ludwig Maximilian University Munich), the UK (Derm4Pets Clinic, Buckinghamshire/Berkshire) and the USA (Animal Dermatology Clinic, Tustin, California) participated.

Forty-eight privately owned dogs with atopic dermatitis were included, of different genders, ages and breeds. The treatment group consisted of 23 dogs classified with either moderate to severe CAD (n=12) or mild CAD (n=11). There were 25 dogs in the placebo group (16 classified with moderate to severe CAD and nine with mild CAD).

Randomization

The dogs were stratified into two subgroups with mild disease characterized prior to treatment by either low lesion scores i.e. a CAD extent and severity index-03 (CADESI-03) < 60 (n=20), or moderate to severe disease (CADESI-03 >60; n=28; Olivry et al., 2008). Separate randomization schedules for both groups and each study centre were created by the study monitor prior to the study according to a computer-generated randomization list[1]. Medication and identically packaged placebos were sent to each study centre and each package was specifically marked and dispensed according to the randomization list.

Inclusion criteria

All dogs had been diagnosed with environmentally-induced atopic dermatitis based on history, clinical signs and rule-out differential diagnoses by appropriate means, such as skin cytology, skin scrapings, elimination diets and/or ectoparasite control measures. Dogs with mild disease were treated exclusively

with topical therapy, either product or placebo. Antihistamines and other topical therapies were discontinued at least 2 weeks prior to starting the study and glucocorticoids and cyclosporin were discontinued at least 6 weeks prior to enrolment.

In the group with moderate to severe CAD, exclusive treatment with placebo or topical fatty acids/essential oils was considered unethical due to the reported limited improvement seen with oral fatty acid supplementation (Mueller et al., 2004 and Olivry et al., 2001b). Concurrent low dose glucocorticoids, antihistamines and topical therapy were permitted if they had been administered at an unchanged dose for more than 12 weeks prior to inclusion and during the trial. Diet changes were not permitted within 3 months prior to or during the study. Allergen-specific immunotherapy was permitted in dogs that had been receiving it for at least 12 months prior to inclusion. Dogs with a history or clinical signs of flea bite hypersensitivity received fipronil spot on (Frontline, Merial) or selamectin spot on (Stronghold, Zoetis) once monthly.

Study protocol

All dogs were treated with a spot-on preparation once weekly for 8 weeks. The owners applied the product on the dorsal cervical area after being given detailed instructions on how to spread the hair coat and apply the product directly onto the skin. Dogs received either a product containing PUFAs (6 mg/mL of α-linolenic and 30 mg/mL of linoleic acid), essential oils (neem oil, rosemary extract, lavender oil, clove oil, tea tree oil, oregano extract, peppermint extract and cedar bark extract) and vitamin E (Dermoscent Essential 6 spot-on, LDCA) or a placebo (bio diffusing agents, Dermoscent, LDCA).

Dogs <10 kg received 0.6 mL weekly; dogs weighing 10-20 kg received 1.2 mL weekly, and dogs of 20-40 kg received 2.4 mL weekly. This protocol was according to the manufacturer's recommendations and the same as the protocol used in a previously published pilot study (Tretter and Mueller, 2011). The commercial product has a distinct odour that was absent from the placebo. However, the owners of placebo treated dogs were not aware of this difference. It was previously established that the odour dissipated within 1 week of application and investigators were unable to detect the odour at the time of scoring, thus keeping the integrity of the blinding intact.

Clinical evaluation

A validated lesion score (CADESI-03; Olivry et al., 2007 and Olivry et al., 2008) was used to determine the severity of skin lesions. If the initial CADESI-03 was $\leqslant$ 60, dogs were considered to have mild CAD (n=20). If the CADESI-03 was > 60, the disease was categorized as moderate to severe (n=28), as previously reported (Olivry et al., 2008). Dogs with moderate to severe disease commenced the study after their clinical signs had improved with other therapies (see above) and they were considered stable. Dogs were evaluated at enrolment and after 8 weeks of treatment. The CADESI-03 score was determined by the clinician at each visit. Similarly, owners completed a validated pruritus score at each visit, scoring pruritus from 0 to10 using a visual analogue scale combined with features of the behaviour and severity-based scales (Hill et al., 2007; Appendix B).

Statistical analyses

Based on data gathered in a recent pilot study (Tretter and Mueller, 2011), it was calculated that with at least 20 dogs in each group (treatment and placebo), a difference of 6 points in CADESI-03 scores and 2 points in pruritus scores could be determined with a power of 90% and a significance level of P<0.05. To ensure similar groups, initial CADESI-03 scores and pruritus scores were compared using Mann Whitney tests. For the same reason, the age and weight of dogs in both groups were compared with an unpaired t test or (if data were normally distributed) or Mann-Whitney U tests (if data were not normally distributed). Gender distribution was analyzed using Fisher's exact tests. Improvements in pruritus and CADESI-03 scores, respectively, were calculated by subtracting the score at enrolment from the score at the end of the study. This was compared between groups using an unpaired t test with Welsh correction (if data were normally distributed), or a Mann-Whitney U test (if data were not normally distributed). The number of dogs improving by at least 50% and the number of dogs deteriorating in the treatment group compared to the placebo group were compared using Fisher's exact tests.

A one-sided *P* value was chosen, as a previously published pilot study had shown improvement in both pruritus and CADESI-03 scores with this therapy (Tretter and Mueller, 2011) and thus deterioration was not expected in the treatment group compared to placebo. Significance for all tests was set at $P<0.05$. The statistical program used was GraphPad Prism 5.0 (GraphPad). Dogs were excluded from the per protocol analysis if they exhibited clinical signs of an adverse reaction to the product, when owner compliance was not satisfactory, or when the clinical signs of atopic dermatitis deteriorated to the point that additional antipruritic therapy was needed. An intention to treat analysis, with the last value carried forward, using all dogs included in the study was performed, as well as a per protocol analysis.

Results

CADESI-03 and pruritus scores

There was no significant difference between treatment and placebo groups with respect to CADESI-03 scores ($P=0.278$) or pruritus ($P=0.909$) at enrolment. There was also no difference between groups in age ($P=0.735$), bodyweight ($P=0.782$) or gender distribution ($P=0.785$). Because two dogs did not complete the study, per protocol analysis was performed on 46 dogs. As the results of the intention to treat analysis and that of the per protocol analysis were similar, only the results of the intention to treat analysis are reported here.

The mean and the confidence intervals of CADESI-03 and pruritus scores pre- and post-therapy are shown in Table 1. Individual improvements in CADESI-03 scores and pruritus scores in each dog were significantly higher in the treatment group than in the placebo group (Mann-Whitney *U* test, $P=0.011$ and $P=0.036$, respectively). The numbers of dogs improving by at least 50% or 90% are listed in Table 2. More dogs showed an improvement of $\geqslant$50% in CADESI-03 and pruritus scores in the treatment group than in the placebo group (Fisher's exact test, $P=0.008$ and $P=0.07$, respectively). Significantly more dogs deteriorated in the placebo group (15/25) compared to the treatment group (5/23; Fisher exact test, $P=0.01$). Raw data are shown in Appendix B: Supplementary Materials.

Table 1.
Data for CADESI-03 and pruritus scores of dogs with atopic dermatitis treated with either a spot-on formulation containing essential fatty acids/essential oils or placebo.

	Treatment Day 0	Treatment Day 56	Improvement [a] with treatment	Placebo Day 0	Placebo Day 56	Improvement [a] with placebo
Total number of dogs	23			25		
Mean CADESI-03 (95% CI)	46 (29-63)	28 (18-39)	18 (4-32)	78 (41-116)	80 (44-115)	-1 (-19-13)
Mean pruritus (95% CI)	5.2 (4.2-6.2)	3.9 (2.7-5.2)	1.3 (0.2-2.4)	5.3 (4.3-6.3)	5.0 (4.1-6.0)	0.2 (-0.7-1.2)
Number of dogs with mild AD	11			9		
Mean CADESI-03 (95% CI)	25 (13-36)	15 (9-22)	9 (-1-20)	22 (11-32)	34 (21-48)	-13 (-21- -5)
Mean pruritus (95% CI)	4.8 (2.9-6.6)	4.0 (1.5-6.0)	1 (-0.9-2.9)	3.8 (2.1-5.5)	4.0 (2.1-5.9)	-0.2 (-2.6-2.2)
Number of dogs with moderate-severe AD	12			16		
Mean CADESI-03 (95% CI)	66 (38-94)	40 (22-58)	24 (-1-50)	110 (58-163)	105 (53-157)	6 (-19-30)
Mean pruritus (95% CI)	5.6 (4.4-6.8)	4.1 (2.5-5.7)	1.5 (0-3.0)	6.1 (5.1-7.2)	5.6 (4.5-6.8)	0.5 (-0.5-1.5)

CADESI-03, Canine atopic dermatitis extent and severity index-03; CI, Confidence interval

a Improvement = Score at the beginning of the trial – Score at the end of the trial.

Table 2.

Numbers of dogs improving by more than 50% and 90% in CADESI-03 and pruritus scores when treated with a spot-on formulation containing essential fatty acids/essential oils or placebo.

	Treatment improvement ⩾ 50%	Placebo improvement ⩾ 50%	Treatment improvement ⩾ 90%	Placebo improvement ⩾ 90%
CADESI-03 (*n*)	8/23	1/25	1/23	0/25
Pruritus score (*n*)	9/23	4/25	2/23	1/25

CADESI-03, Canine atopic dermatitis extent and severity index-03.

Table options

Adverse effects and exclusions

All except two dogs completed the study. These had moderate to severe clinical signs and both deteriorated during the first 4 weeks of the study, requiring their concurrent therapy to be changed. One of those dogs was in the treatment group and one was in the placebo group. Adverse effects were not observed in any of the treated dogs.

Discussion

This study demonstrated that the clinical signs of atopic dermatitis in dogs with stable CAD that met the study entry criteria significantly improved after eight weekly topical treatments of a commercially available compound containing PUFAs and essential oils. The degree of improvement was similar to another randomized, placebo-controlled study where 29 dogs received oral fatty acid supplementation for 10 weeks and showed significant improvement (Mueller et al., 2004). That study used a different scale to measure outcomes, as it preceded the use of the CADESI-03 and the visual analogue pruritus scale for use by dog owners (Mueller et al., 2004).

The results of the present investigation support the findings of a recent pilot study using the same product (Tretter and Mueller, 2011) and also studies evaluating oral fatty acid supplementation (Olivry et al., 2010). PUFAs are thought to have lower efficacy than glucocorticoids and cyclosporin (Olivry et al., 2010), but they are a safe alternative to other anti-inflammatory therapies. Adverse effects associated with their use are rare and usually mild (Mueller et al., 2004 and Olivry et al., 2010), which is particularly important in the long-term treatment of chronic diseases such as CAD. In this work, no adverse effects were noted with short-term use (8 weeks). Widespread use of the product over longer periods of time is needed to make more definitive statements regarding safety.

As this is the first double-blinded, placebo-controlled study evaluating topical therapy with a commercial product containing essential oils and PUFAs, the only comparison possible is with oral PUFA supplementation. There are many studies using oral PUFA supplementation, but only a few that are placebo-controlled and double-blinded. In one such study, there was a significant improvement of clinical signs with commercially available EPA and DHA preparations (Mueller et al., 2004). In another controlled study based on the measurement of serum arachidonic acid before and after the trial, dogs with early CAD showed more improvement than dogs with a longer history of CAD (Abba et al., 2005).

Direct comparison of an oral and topical product is not possible, but our study provides evidence that the efficacy of topical therapy with essential oils and PUFAs appears to be comparable to that reported for studies evaluating oral PUFAs (Mueller et al., 2004 and Saevik et al., 2004). With oral fatty acid supplementation, approximately half of the dogs treated with daily fatty acids improved by 50% or more compared to only 10% in the placebo group in an earlier study (Mueller et al., 2004). In the current work, the corresponding results were in the same range for CADESI-03 and pruritus scores, suggesting both types of treatment are suitable for the treatment of CAD, but the success rate for either one is not as high as that for glucocorticoids or cyclosporin (Olivry et al., 2010 and Steffan et al., 2006).

It was recommended a decade ago that PUFA supplementation should be administered for at least 12 weeks before assessing the success of treatment (Olivry et al., 2001b). This was based on the pharmacokinetics of oral PUFAs (Campbell et al., 1995 and Campbell and Dorn, 1992). However, other authors observed effects with daily PUFA supplementation as early as 2 weeks after the initiation of therapy (Olivry et al., 2010, Scott et al., 1992 and Scott et al., 1997). In our study, an 8-week supplementation period was chosen because the clinical effects in a pilot study were noted after 8 weeks of administration (Tretter and Mueller, 2011).

In the present study, a validated pruritus score and a CADESI-03 were used. Pruritus and skin lesions are typically considered the most relevant parameters in studies evaluating CAD (Olivry et al., 2010). The scores for lesions and pruritus have been previously validated (Hill et al., 2007, Olivry et al., 2007 and Olivry et al., 2008). The number of dogs improving by more than 50% and 90%, respectively, was always higher in the treatment group than in the placebo group for both pruritus and CADESI-03 scores. However, in the placebo group more dogs improved in pruritus scores than in CADESI-03. The improvement in pruritus scores could be perceived rather than real and might provide evidence for the more subjective nature of the assessment of pruritus.

PUFAs are considered less efficacious than, for example, glucocorticoids (Olivry et al., 2010) or cyclosporin (Steffan et al., 2006) in the treatment of CAD, but have been shown to be successful as adjunctive therapy (Saevik et al., 2004). For this reason, additional medications were permitted in dogs with moderate-severe atopic dermatitis, as outlined above. In addition, it was considered unethical to treat dogs with more severe disease exclusively with topical fatty acids/essential oils. Dogs with a CADESI-03 of > 60 have been classified as having moderate to severe atopic dermatitis (Olivry et al., 2008). Since the clinical signs in those dogs were unlikely to be controlled by sole therapy with PUFAs/essential oils, the use of concurrent medication was considered ethical and justified. As the dose of concurrent medications was not changed for the 12 weeks preceding the study or during the study, those drugs are unlikely to have influenced the study outcome.

It is not clear how well spot-on preparations containing fatty acids distribute in the epidermis and how long possible changes in epidermal ceramide composition last. One study reported a significant increase in free ceramides at the application site 3 days after the last treatment after twice weekly application of a topical spot-on preparation containing ceramides and free fatty acids for 3 weeks (Popa et al., 2012). The clinical improvement seen in dogs with multifocal to generalized skin disease treated with such products further supports some effect on the epidermis, but more studies are needed to provide details regarding the distribution and mechanism of action of topical essential oils and PUFAs in dogs.

Conclusions

Based on the findings in this study, the application of a spot-on containing PUFAs and essential oils was beneficial in alleviating the clinical signs of CAD. As complete remission was not achieved in the vast majority of dogs, it seems most useful as an adjunctive therapy in this disease.

Conflict of interest statement

The study was financed by Laboratoire de Dermo-Cosmetique France, which had no influence on study design, data evaluation or manuscript preparation. Dr. Blaskovic was financially supported by LCDA France. None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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1 See: http://graphpad.com/quickcalcs/randomN1.cfm (last accessed 15 October 2013)