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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.

Introduction

Canine atopic dermatitis (CAD) is a commonly presented disease in veterinary practice (Scott and Paradis, 1990) and is associated with pruritus (Saridomichelakis et al., 1999; Griffin and DeBoer, 2001) and skin lesions (Griffin and DeBoer, 2001; Favrot et al., 2010). 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; 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 (Olivry and Hill, 2001; Marsella et al., 2006).

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; 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 and Dorn, 1992).

In contrast to many other symptomatic therapies for CAD, oral supplementation with PUFAs rarely causes adverse effects (Olivry

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et al., 2001; Mueller et al., 2004), 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 (Scott and Miller, 1993; Bond and Lloyd, 1994; Saevik et al., 2004).

Studies on the use of oral fatty acid supplementation have been published (Mueller et al., 2004; 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; 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 (Olivry et al., 2001; Mueller et al., 2004). 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.

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

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, 2008) was used to determine the severity of skin lesions. If the initial CADESI-03 was ⩽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 to 10 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.