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Evaluation of cyclosporine-sparing effects of polyunsaturated fatty acids in the treatment of canine atopic dermatitis

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ABSTRACT

A randomised, double-blinded, placebo-controlled multicentre trial was conducted in 36 dogs with atopic dermatitis to evaluate the cyclosporine-sparing effect of polyunsaturated fatty acids. Dogs were stable on their individual cyclosporine dosage and received either a mainly omega-3 fatty acid product with a minor omega-6 fatty acid fraction or placebo, orally for 12 weeks. Dogs were examined every 4 weeks and the Canine Atopic Dermatitis Extent and Severity Index (CADESI-03) was determined by a clinician. Pruritus, quality of life, global condition and coat quality were scored by the owner. If the dog's CADESI-03 and/or pruritus score improved by at least 25% compared with the previous visit, the cyclosporine dosage was decreased by approximately 25%. If the scores deteriorated by at least 25%, the cyclosporine dosage was increased by the same percentage.

The median daily cyclosporine dosage/kg bodyweight decreased in the active group from 4.1 mg to 2.6 mg and in the placebo group from 3.5 mg to 3.3 mg over the study period. The difference between the two groups was significant ($P = 0.009$). The improvement in median pruritus score from inclusion to completion was significantly greater in the active group than in the placebo group ($P = 0.04$). There was no significant difference in CADESI-03 changes between groups ($P = 0.38$). The results of this study indicate a cyclosporine-sparing effect of a mainly omega-3 fatty acid supplement in dogs with atopic dermatitis.

Introduction

Canine atopic dermatitis (CAD) is a common skin disorder in small-animal practice (Scott and Paradis, 1990; Hill et al., 2006) and is defined as a hereditary predisposition to develop pruritic inflammatory skin disease associated with IgE antibodies, which typically target environmental allergens (Halliwell, 2006). The most consistent clinical feature is pruritus of the face, ears, paws, limbs and ventrum where secondary lesions may also arise (Griffin and DeBoer, 2001).

The sole causal treatment for CAD is allergen-specific immunotherapy (Mueller and Bettenay, 1996; Loewenstein and Mueller, 2009). However, response to this treatment may take several months (Loewenstein and Mueller, 2009) and it is not effective in all dogs (Mueller and Bettenay, 1996). Consequently, atopic dogs are often treated symptomatically with glucocorticoids (Olivry and Sousa, 2001), cyclosporine (Steffan et al., 2006), antihistamines (DeBoer and Griffin, 2001), oclacitinib (Cosgrove et al., 2013) and polyunsaturated fatty acids (PUFA) (Mueller et al., 2004; Olivry et al., 2010). Cyclosporine has proved to be no less effective than glucocorticoids in reducing the clinical signs of CAD (Olivry et al., 2002; Steffan et al., 2003).

PUFA can be divided into omega-3 and omega-6 fatty acids and are considered a safe therapeutic option for the treatment of CAD (Mueller et al., 2004; Olivry et al., 2010). The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may modulate eicosanoid synthesis, as they compete with arachidonic acid (AA) for the enzymes cyclooxygenase and 5-lipoxygenase, leading to an increased production of anti-inflammatory eicosanoids instead of proinflammatory eicosanoids derived from AA (Vaughn et al., 1994). PUFA may also inhibit cellular activation (Stehle et al., 2010) and proinflammatory cytokine secretion (Caughey et al., 1996; Novak et al., 2003) as well as stabilise the epidermal lipid barrier (Hansen and Jensen, 1985).

PUFA appear to be insufficient as sole therapy for CAD (Olivry and Sousa, 2001; Olivry et al., 2001, 2010) although a steroid-sparing

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effect of PUFA has been shown (Saevik et al., 2004), making PUFA supplementation with glucocorticoid therapy reasonable. To the authors' knowledge, there are no published data on the cyclosporine-sparing effects of PUFA in the treatment of CAD. The purpose of this study was to evaluate whether orally administered PUFA (Omega-3 Support, WDT)[1] are effective in reducing cyclosporine (Atopica, Novartis) dosage in atopic dogs.

Materials and methods

Study population

Dogs with atopic dermatitis were eligible for inclusion and were diagnosed by history, clinical examination and ruling out differential diagnoses with tests and treatments such as flea control, an elimination diet of 6–8 weeks (home cooked or commercial, containing food proteins that were novel to each dog; Favrot et al., 2010) and skin scrapings or trial therapy against superficial mites as indicated (DeBoer and Hillier, 2001; Olivry, 2010).

All dogs were stable on their individual cyclosporine (Atopica, Novartis) dose for at least 8 weeks prior to inclusion in the study. Other medications were permitted unchanged in the 8 weeks prior to and during the study. Dogs with a proven food adverse reaction had to be on the same diet for at least 3 months prior to inclusion and during the study. Allergen-specific immunotherapy was permitted as long as it was initiated more than 12 months before inclusion and not changed during the study. Oral and topical fatty acids were withdrawn for at least 12 weeks and 8 weeks before commencement of the study, respectively.

Dogs with skin infections in need of antibiotic therapy at recruitment were excluded. Serious adverse reactions to the study-drugs as well as lack of owner compliance were further reasons for withdrawal from the study.

Study design

The study was carried out as a randomised, placebo-controlled, double-blinded multi-centre study. The study protocol was approved by the Ethics Committee of the Centre for Clinical Veterinary Medicine, LMU Munich (number 8-20-06-13, dated 3 July 2013). Dogs were assigned to one of two treatment groups using a computer-generated randomisation list. Study medications were labelled A, B, C, D with two letters assigned for each group and neither dog owners nor evaluating clinicians were aware of the coding.

Participating clinics

Participating clinics were referral dermatology clinics in Germany (Prof. Dr. Ralf Mueller, Medizinische Kleintierklinik LMU Munich; Dr. Monika Linek, Tierärztliche Spezialisten Hamburg; Dr. Christine Löwenstein, Tierärztliche Gemeinschaftspraxis Dr. David, Dr. Krützfeldt Frankenthal; Dr. Anja Röthig, Klinik für Kleintiere, Justus-Liebig-Universität Giessen; Drs. Kerstin and Brett Wildermuth, Tierdermatologie Dr. Wildermuth Wiesbaden; Drs. Sonya Bettenay and Nina Glos, Tierärztliche Fachklinik für Kleintiere Haas und Link Germering), France (Dr. Emmanuel Bensignor, Centre Hospitalier Vétérinaire Paris), Austria (Dr. Lucia Panakova, Vetmeduni Vienna) and Switzerland (Dr. Claudia Nett, Dermatologie und Allergologie für Tiere Huenenberg). Clinical evaluations were performed by participating dermatology specialists.

Clinical evaluation

Dogs were examined on the day of inclusion before receiving study medications (week 0) and after 4, 8 and 12 weeks of therapy. At each visit, a dermatologist examined the animal and determined a validated lesion score, the Canine Atopic Dermatitis Extent and Severity Index (CADESI-03) (Olivry et al., 2007, 2008). Briefly, 62 body sites were evaluated for marks of acute inflammation (erythema), chronic inflammation (lichenification), trauma (excoriation) and alopecia on a scale of 0 (non-existent) to 5 (severe) and the additive total score was calculated. Additionally, owners determined the intensity of their dog's pruritus using a validated pruritus severity visual scale ranging from 0 (pruritus not observed) to 10 (severe pruritus) (Hill et al., 2007; Rybnicek et al., 2009). Owners also completed a validated quality of life score (Noli et al., 2011a, 2011b) at every visit, where 0 points indicated 'no disturbing influence' and 45 points indicated a 'great disturbing influence' on the quality of life. They also judged the dog's global condition compared to the previous visit from 'deteriorated' (total minimum of –2 points) to 'strongly improved' (total maximum of 5 points) and evaluated the coat quality on a scale from dull/greasy (–1 point) to shiny (2 points). All adverse events occurring during the study were reported in accordance with the current pharmacovigilance regulations.

[1] In other countries, also known as Omevio, Novartis Animal Health.

Intervention

Dogs received either a preparation of plant oil and fish oil containing omega-3- and omega-6 polyunsaturated fatty acids in a ratio of 3.75:1 (Omega-3 Support, WDT) or placebo (paraffin oil for medical purposes) daily for 12 weeks at a dose of 3 mL/10 kg/day, given with food by the owner. Each 3 mL of the PUFA supplement contained approximately 360 mg alpha-linolenic acid (ALA), 410 mg eicosapentaenoic acid (EPA), 249 mg docosahexaenoic acid (DHA) and the omega-6 fatty acids linoleic acid (LA) and docosapentaenoic acid (DPA) in minor fractions. CADESI-03 and pruritus scores were determined every 4 weeks. If the dog showed an improvement of either CADESI-03 or pruritus or both of at least 25% compared with the previous visit, the dose of cyclosporine was decreased by approximately 25%. If lesions or pruritus deteriorated by 25% or more, the dose of cyclosporine was increased again by approximately 25%. Dosage changes were performed as shown in Fig. 1.

Dogs were evaluated for cutaneous infections by clinical examination and cytological evaluation of impression smears at each visit. If a skin infection occurred during the study, routine antimicrobial therapy was administered. Antibiotics were discontinued during the last 3 weeks of the study to avoid influence on clinical and pruritus scores. All patients received a spot-on treatment for flea control containing pyriprole (Prac-Tic, Novartis) once monthly.

Statistics

Primary outcome measure was the change of the daily dose of cyclosporine, which was compared before and after the trial in both groups. The dose of cyclosporine at the end of the trial was the dose the dog would have gone home with if the trial were to be continued. The secondary outcome measures were CADESI-03, pruritus score, quality of life score, coat quality and the global assessment after compared to before the trial. The changes in the treatment group (week 0–week 12) were compared with the corresponding changes in the control group using a Mann–Whitney test. A $P < 0.05$ was considered significant. For the comparison of cyclosporine dose changes the P value was one-sided, for all other comparisons a two-sided P-value was chosen. In addition to a per-protocol analysis, an intention-to-treat with the last value carried forward analysis was performed.

Results

Patients

Thirty-six dogs were enrolled in the study. There were 20 dogs in the active group and 16 in the placebo group. Of these, 34 completed the trial. One dog in the placebo group was euthanased due to an intervertebral disc prolapse, while another in the same group failed to attend the final study visit for unspecified reasons.

The dogs' ages ranged from 12 months to 13 years with a mean of 6 years. Twenty-one dogs were female (nine neutered) and 15 were male (one neutered, 14 intact). Twenty-one different pure breeds and five mixed breeds were represented. The mean bodyweight was 19.3 kg (range 5.5–54.6 kg). Of the 36 atopic dogs, 22 were solely allergic to environmental allergens, while 14 dogs also indicated signs of food allergy and were therefore on a special diet. All dogs showed allergy symptoms throughout the year.

For detailed information on concurrent medications, see Appendix A: Supplementary material. There were no significant differences between the active and placebo groups in age, weight and dose of cyclosporine of the study population.

Clinical evaluation

The median cyclosporine dosage in the active group was 4.1 mg/kg/day at the beginning of the study, and 2.6 mg/kg/day at the end of the study. In the placebo group, the cyclosporine dose was 3.5 mg/kg/day at inclusion and 3.3 mg/kg/day at completion. The mean and median decreases in the cyclosporine dosage in the active were 0.85 mg/kg and 0.32 mg/kg, respectively. For the placebo group the respective values were 0.06 mg/kg and 0.0 mg/kg. As the statistical evaluation of the intention-to-treat analysis and the per-protocol analysis were similar, only the former results are shown. The difference in the cyclosporine dosage between the two groups at inclusion compared to completion was significant (Mann–Whitney test, $P = 0.009$). For the complete data set, see Appendix A: Supplementary material.