The Veterinary Journal 197 (2013) 280–285

Contents lists available at SciVerse ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

# Efficacy of a new topical cyclosporine A formulation in the treatment of atopic dermatitis in dogs

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ARTICLE INFO

*Article history:*
Accepted 21 February 2013

*Keywords:*
Topical
Cyclosporine
Dog
Atopic dermatitis
Clinical trial

ABSTRACT

Topical treatment with cyclosporine A (CsA) has recently become possible with the development of novel nanotechnology pharmaceutical formulations of CsA able to penetrate through the epidermis providing good absorption and dermal action. The aim of this multicentre, blinded, parallel, randomized, placebo controlled trial was to evaluate the efficacy of a new topical CsA formulation in dogs with atopic dermatitis (AD). Dogs ($n = 32$) with severe and moderate clinical signs of non-seasonal AD, but few localized lesions, were randomly allocated to receive topical CsA (17 dogs) or placebo (15 dogs) and were treated twice a day for 6 weeks. Before and 21 and 45 days after starting the treatment, the severity of a previously selected skin lesion was evaluated according to a dermatological scoring system. Owners using a visual analogue scale also assessed pruritus weekly and effectiveness of the treatment was defined as a reduction of at least 50% in these variables after 45 days.

After 21 and 45 days the lesion severity score in animals treated with CsA was significantly lower than at baseline ($P < 0.01$, both times). In contrast, the animals on placebo showed no significant improvement at days 21 or 45. The percentage of dogs with an effective reduction in pruritus at the end of the trial was 87.5% and 28.6% in the CsA and placebo groups, respectively. These results suggest that topical administration of CsA is effective in reducing the severity of skin lesions and pruritus in dogs with moderate to severe AD as soon as 3 weeks after starting treatment.

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## Introduction

The prevalence of atopic dermatitis (AD), the second most common form of allergic dermatitis in dogs, has risen in recent decades, and about 10% of dogs aged from 1 to 3 years are now thought to be affected with the condition (Bensignor, 2010). The pathogenesis of AD has not been fully elucidated and the treatment options available are limited. Although allergen-specific immunotherapy remains the treatment of first choice in some cases because it is the safest way to modulate the immune response (Olivry et al., 2010a), alternative treatments with immunosuppressive agents are also available and offer advantages, such as easy dosing protocols and faster response rates (Nuttall et al., 2009, 2012; Deboer et al., 2002). For this reason, immunosuppressant drugs such as glucocorticoids or calcineurin inhibitors are also now considered well-established treatments for AD.

Cyclosporine A (CsA) was the first immunosuppressant found to act selectively on T cells (White et al., 1979). CsA forms a complex with cyclophilin, an intracellular immunophilin, and inhibits the activity of calcineurin phosphatase so depleting lymphocytes and macrophages and inhibiting the activation of T cells, natural killer cells, and antigen-presenting cells (Gupta et al., 1989; Stepkowski, 2000; Giese et al., 2004; Ferraccioli et al., 2005). CsA also inhibits keratinocyte proliferation (Won et al., 1994; Gottlieb et al., 1995), inhibits the release of histamine from mast cells (Amon, 1992; Sperr et al., 1996; García et al., 1998), and down-regulates the expression of cellular adhesion molecules on dermal capillary endothelium (Mrowietz and Ruzicka, 1999).

The potent immunosuppressive activity of oral CsA is responsible for its efficacy but also for toxic effects, which are

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http://dx.doi.org/10.1016/j.tvjl.2013.02.018

dose-dependent and related to the duration of therapy but reversible. However, structural renal abnormalities and bacterial infections may persist (Radowicz and Power, 2005). Therefore, when a condition is chronic and CsA must be used long term, the potential risk of toxicity increases (Ring et al., 2008; Heinrich et al., 2011).

CsA was approved by the United Sates Food and Drug Administration for the treatment of psoriasis in humans in 1997. In Europe, CsA is the only immunosuppressant drug approved for the short-term treatment of severe human AD that cannot be controlled with topical agents (Bussmann et al., 2009). In dogs, oral CsA has been widely used to control AD (Olivry et al., 2002a), but adverse effects have been reported in up to 81% of treated dogs (Nuttall et al., 2012). Another problem of CsA is its high cost, especially in large-breed dogs, so its use when there are only localized lesions is questionable. Although topical administration of CsA would seem to offer a more rational use of this drug, such use has not been feasible to date because only a lipophobic conformation has been available (CsA $\log P = 2.92$).

Nanotechnology, a field devoted to the manipulation of matter at a scale <1 μM (i.e. at the level of atoms and molecules), has enabled the development of a lipophilic CsA emulsion. We prepared nanocapsules of chitosan, a mucoadhesive compound chosen to protect CsA from degradation and create a film on the skin surface to enhance penetration. These nanocapsules were incorporated into an oil-in-water emulsion (CsA concentration, 2.5%) for use in the present study; the excipients were poloxamer 188, castor oil and soy lecithin. This CsA nanocapsule preparation was designed to be sprayed on the skin, where it would quickly penetrate the epidermis and act within the dermis. Preliminary pharmacokinetic studies performed in our laboratory confirmed that the CsA nanocapsules accumulate in the skin without reaching the bloodstream, thus avoiding systemic immunosuppression, gastrointestinal disorders and other adverse effects (unpublished results). The aim of this pilot trial was to evaluate the efficacy of this formulation in the treatment of localized AD in 17 non-seasonal atopic dogs.

## Materials and methods

### *Study design and subjects*

This 45-day, double-blinded multicentre, multi-investigator, randomized placebo-controlled parallel-group (1:1) trial was reviewed and approved by the Spanish Agency for Medicines and Health Care Products (AEMPS) (protocol number 233/ECV).

The trial was carried out in two veterinary teaching hospitals and four private dermatology clinics in Spain. Thirty-two dogs were enrolled: 15 received placebo and 17 the active treatment. Inclusion criteria were a clinical diagnosis of non-seasonal AD according to the criteria of Willemse (1986) and exclusion of other allergic dermatoses based on absence of response to treatment for flea infestation (at least 8 weeks) and to an elimination diet (at least 6 weeks) before the start of the trial. Dogs were older than 12 months of age and presented with AD lesions on the front or hind limbs, including axilla or groin. Exclusion criteria included pregnancy or lactation, seasonal signs of AD involving flea infestation or food allergens, presence of bacterial or *Malassezia* skin infections or other infestations causing pruritus (e.g. mites), and being treated with one or more of the following: topical glucocorticoids, oral antihistamines or fatty acids within 2 weeks of enrolment, oral glucocorticoids, oral CsA or allergen-specific immunotherapy within 4 weeks of enrolment and injectable glucocorticoids within 8 weeks of enrolment. Concomitant treatments that could have an effect on AD and that would affect the assessment of the effectiveness of the products under investigation (topical CsA or placebo) were not allowed during the trial.

Blinding was guaranteed using identical emulsion spray containers and formulations with similar appearance for CsA and placebo. Each product was coded (labelled T02 and T01, respectively) to ensure that the researchers and staff involved in the evaluations would work under the same blinded conditions as the owners. Allocation to one of the two treatments was based on a random number generation system. The treatment codes were available to the trial's sponsor and the monitor but could only be consulted in cases of emergency. Such consultation never became necessary.

### *Study procedures and data collection*

The animals underwent physical examination and if it was established that they met the criteria for inclusion, the investigator recorded weight, age, breed, sex and other relevant data. A complete dermatological examination was carried out by a veterinarian and the areas affected by AD were recorded. The intensity of pruritus was assessed on a visual analogue scale (VAS) comprising a 10 cm long line (oriented horizontally) on which owners indicated the intensity of pruritus by crossing the line at the point that corresponded to the severity of the dog's pruritus. Descriptors were indicated at the ends (0 and 10 cm), but the line was not graded to facilitate a more realistic measure of the symptom that would not be influenced by previous measurements. Assessments were converted to a number and noted.

The researcher evaluated and recorded baseline severity levels of erythema, lichenification, and excoriations for the lesional area to be treated. These clinical signs were evaluated on a scale of 0–3 points (Table 1) for a maximum of 9 points per lesion and patient. At this time one lesion scored $\geqslant 6$ was selected for later assessment of outcome and its location, surface area ($cm^2$), and severity score were recorded. The allocated product was then applied by a member of the clinic's staff to limb, axilla and/or groin lesions; this application served to show the owner how to use the spray device, which delivered 0.8 mL with each spray. The affected areas were sprayed once or twice, depending on the size of the lesion; the nozzle was held at a distance of approximately 20 cm from the skin. Afterwards at home, the owner applied the treatment twice a day (approximately every 12 h) for a period of 45 ± 2 days. Owners were told to wear gloves when spraying the product and to distract the dog for a few minutes afterwards until the product was completely absorbed. Baths were not permitted 3 h before or 3 h after treatment.

Each owner was given a form to record the dose applied (one or two sprays) to be completed every day and to show to the researcher at every visit in order to evaluate compliance. For animal welfare reasons, other lesions on the animal could be treated even though they were not included in the outcome evaluation.

### *Outcome measures, endpoints, and withdrawals*

Effectiveness of treatment was assessed 21 and 45 days (endpoint) after the baseline treatment. As at baseline, the researcher evaluated the severity of erythema, lichenification, and excoriations on a scale of 0–3 points. The owner also estimated the severity of pruritus on the VAS at each visit and a score (0–10) was noted. For purposes of the intention-to-treat analysis (including all initially enrolled dogs), animals withdrawn early for reasons of severe pruritus were assigned the same VAS score the owner reported at the time the animal left the study.

Animals with a higher lesion severity score on day 21 than at baseline were removed from the trial and the treatment was considered to have failed. A higher lesion score on day 45 (endpoint) than at baseline also indicated therapeutic failure. Once failure had been recorded at either visit, the animal could be treated with what the researcher considered appropriate. Animals could also be withdrawn for other reasons, such as use of prescribed concomitant treatments, concomitant disease that could interfere with the assessment of CsA efficacy (e.g., bacterial pyoderma, *Malassezia* dermatitis, etc.), or the owner's decision to discontinue participation.

Efficacy within groups was defined by the rates of lesion improvement from baseline according to the dermatological scoring system for lesion severity or by associated pruritus on days 21 and 45 for each treatment group. The mean lesion severity scores on days 21 and 45 were then compared between treatments. For pruritus control, efficacy was defined as a reduction from baseline in the VAS score of $\geqslant 50\%$ on days 21 and 45; the percentages of animals meeting that target were compared between groups.

For efficacy comparisons, data for the enrolled dogs were divided into two groups for analysis per treatment protocol and per intention to treat. The per-protocol analysis included data for all animals reaching the end of the treatment protocol (45 days); this dataset comprised 23 cases (14 in the CsA group and 9 in the placebo group). The intention-to-treat analysis was based on all 32 cases (17 in the CsA group and 15 in the placebo group). The per-protocol analysis included only dogs whose owners adhered to the protocol and continued in the trial.

### *Statistical analysis*

The statistical analysis was performed using SAS software (v.9.1, SAS Institute). Results are expressed as group means (± standard deviations). Statistical significance was set at a level of $P \leqslant 0.05$. The between-group comparisons of quantitative response variables were performed with ANOVA and the Mann–Whitney–Wilcoxon and Kruskal–Wallis tests. Compliance with conditions for applying these tests was checked with the Shapiro–Wilk and Kolmogorov–Smirnov normality tests and the Levene test for homogeneity of variances. Within-group comparisons of quantitative response variables were accomplished with ANOVA for paired measures and the Wilcoxon test for paired measures. Compliance with conditions for these tests was also checked with the Shapiro–Wilk and Kolmogorov–Smirnov normality tests.

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