

Comparable efficacy of a topical 0.0584% hydrocortisone aceponate spray and oral ciclosporin in treating canine atopic dermatitis

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Conflict of Interest

C.A.R. is an employee of Virbac SA. T.J.N., N.A.McE., E.B., L.C. and C.L. have received other unrelated funding from Virbac SA. T.J.N. and E.B. have also received unrelated funding from Novartis Animal Health. Apart from C.A.R., none of the authors has any direct or indirect financial interests in the products used in this study.

Abstract

This study compared the efficacy of a 0.0584% hydrocortisone aceponate (HCA) spray (Cortavance®; Virbac SA) and ciclosporin (Atopica®; Novartis Animal Health) in canine atopic dermatitis in a single-blind randomized controlled trial. Dogs received HCA (two sprays/100 cm²; $n = 24$) or ciclosporin (5 mg/kg; $n = 21$). Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03, pruritus (visual analog scale with grade descriptors) and owner scores (5-point scales) were recorded every 28 days for 84 days. Intention-to-treat data were analysed. CADESI-03 and pruritus significantly decreased over time ($P < 0.0001$), but there was no difference between the treatment groups ($P = 0.91$ and $P = 0.52$, respectively). Similar proportions of HCA- and ciclosporin-treated dogs achieved $\geq 50\%$ reductions in CADESI-03 and pruritus scores at 28 days (CADESI-03 58.3 and 57.1%, $P = 0.76$; pruritus 33.3 and 38.1%, $P = 1.0$), 56 days (CADESI-03 70.8 and 81.0%, $P = 1.0$; pruritus 62.5 and 57.1%, $P = 1.0$) and 84 days (CADESI-03 75 and 85.7%, $P = 0.72$; pruritus 65.2 and 57.1%, $P = 0.76$). The CAD-ESI-03 and pruritus scores were close to equivalence (0.47 and 0.51, respectively). By 84 days, every-other-day or twice-weekly therapy was achieved in 13 of 24 HCA- and 12 of 21 ciclosporin-treated dogs ($P = 0.85$). There were no significant differences in scores for efficacy ($P = 0.82$), tolerance ($P = 0.62$) and ease of administration ($P = 0.25$). Scores for tolerance (0.49

and administration (0.46) were close to equivalence. The score for efficacy favoured HCA (0.68). Mild adverse events were noted in six of 21 ciclosporin and none of 24 HCA dogs ($P = 0.008$). Five HCA-treated dogs and three ciclosporin-treated dogs were prematurely withdrawn ($P = 0.7$). In conclusion, HCA and ciclosporin proved equally effective in treating canine atopic dermatitis for up to 84 days.

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Introduction

Canine atopic dermatitis (cAD) is a common, chronic, inflammatory dermatosis.¹ It has become clear that cAD is a complex, multifactorial disease involving interactions between skin structure, the immune system and environmental influences. The complex pathology makes cAD a challenging disease to manage. Treatment options include managing flare factors, bathing and skin care, allergen avoidance, allergen-specific immunotherapy and essential fatty acids, but many atopic dogs require long-term anti-inflammatory medication.^{2,3}

Ciclosporin (Atopica®; Novartis Animal Health, Basel, Switzerland) is a lipophilic cyclic polypeptide with powerful immunosuppressive properties. It is licensed for the treatment of cAD in many countries. Reviews of therapeutic interventions for cAD have concluded that there is good evidence of high efficacy.^{3–6} Randomized controlled trials (RCTs) have demonstrated that oral ciclosporin at 5 mg/kg once daily is at least as effective as prednisolone and methylprednisolone.^{5–8} Mean reductions in lesion scores ranged from 52 to 67% and those in pruritus scores from 45 to 78%.^{7–10} Ciclosporin appears to be well tolerated; adverse effects have been reported in up to 81% of treated dogs, but these are mostly mild to moderate, short-duration gastrointestinal upsets.^{5–11} Less common adverse effects can include persistent anorexia, vomiting and diarrhoea, gingival hyperplasia, hirsutism, verrucose papillomatosis, lameness, insulin resistance, allergic reactions and seizures.^{3,5,11} These, however, usually resolve on lowering the dose and/or withdrawing the drug.

The topical diester glucocorticoid hydrocortisone aceponate (HCA; Cortavance®; Virbac SA, Carros, France) is a 0.0584% spray formulation licensed in many countries (although not in the Americas) for up to 70 days treatment of pyotraumatic dermatitis, flea allergic dermatitis and other inflammatory dermatoses in dogs. Nonhalogen-

ated, diester topical glucocorticoids avoid many of the adverse effects seen with traditional topical glucocorticoids by virtue of their metabolism into largely inactive moieties within the skin.^{12,13} The absence of a halogen at C6, C9 or C21 is associated with better local and systemic tolerance, acetate esterification at C21 increases stability, and propionate esterification at C17 enhances anti-inflammatory activity. Double esterification also enhances penetration of the drug through the stratum corneum and ensures specific metabolism in the deep dermis. This minimizes effects on hair follicles, dermal fibroblasts and blood vessels, decreasing the likelihood of local cutaneous and systemic adverse effects.^{12,13} An RCT demonstrated good efficacy in cAD; mean reductions in lesion scores and pruritus were 61.4 and 38.8%, respectively, with the majority of dogs achieving >50% reductions.¹⁴ Hydrocortisone aceponate appears to be well tolerated; no adverse effects were seen after 70 days treatment in the RCT¹⁴ or after 8 weeks treatment of healthy dogs,¹⁵ but a significant decrease in dermal thickness was noted after 14 days treatment in another study.¹⁶ Recent practice guidelines recommended the use of this product in managing both acute and chronic cAD.³

The RCT¹⁴, however, evaluated HCA against a placebo spray. Comparison against a placebo can overestimate treatment effect, and it is useful to compare novel treatments against an established active control of known efficacy. The aim of this single-blind RCT, therefore, was to compare the efficacy of HCA and ciclosporin in the treatment of cAD. Ciclosporin was chosen as the active control because it is licensed for the management of cAD and has a known, published evidence base for efficacy and safety. Comparison with a 1% triamcinolone spray (Genesis®; Virbac Animal Health, Fort Worth, TX, USA) would have been useful, but this product is not licensed or available in Europe. Systemic glucocorticoids were not included as an active control because of the risk of adverse effects and owner reluctance to use this medication.

Materials and methods

Study patients

The study was performed in accordance with ethical guidelines laid down by The University of Liverpool and Virbac SA. Dogs with a clinical diagnosis of cAD according to accepted criteria^{17,18} were recruited from five European dermatology referral centres (in the UK, Germany, France and Italy). It was estimated that with a mean baseline Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03¹⁹ score of 120 and a mean 60% reduction in the treatment groups with an SD of $\pm 30\%$, 25 dogs in each group would be required to detect significant differences in response with >95% power.²⁰ With the actual CADESI-03 outcomes and intention-to-treat data, the calculated power of the study was 94%.²⁰

Trial protocol

Dogs with cAD that fulfilled the entry criteria (Table 1) were randomly allocated to receive either 0.0584% HCA or ciclosporin according to a computer-generated random sequence established before the trial. Treatment allocation and compliance assessments were made by a dispenser who did not participate in any clinical assessments. Owners were instructed to apply the spray once daily to affected skin only from 10 cm away at a dose rate of two sprays per 100 cm² of affected skin. The ciclosporin was administered at 5 mg/kg orally once daily on an empty stomach, although administration with food

Table 1. Inclusion and exclusion criteria

Inclusion criteria

1. At least 18 months of age
2. History of perennial pruritus
3. Clinical diagnosis of atopic dermatitis
4. No response to a minimum 6 week novel (home-cooked or commercial) or hydrolysed exclusion diet. Dogs should be stabilized on their usual diet for at least 2 weeks prior to the trial, which should be maintained during the study
5. No response to a veterinary-approved flea-control regimen for at least 8 weeks and monthly flea control maintained throughout the trial
6. Sarcoptic mange excluded by trial therapy and/or negative serology
7. CADESI ≥ 16 (i.e. at least mild atopic dermatitis as assessed by CADESI-03)
8. Allergen-specific immunotherapy permitted if used for >12 months, the dose remains unchanged for 6 months, the clinical signs are stable and the regimen is maintained during the trial
9. Essential fatty acids permitted if in use for >8 weeks, the clinical signs are stable and the dosing regimen is maintained during the trial
10. Owner's written informed consent has been obtained

Exclusion criteria

1. Clinical evidence of ectoparasite infestation
2. Clinical evidence of bacterial or fungal infections
3. Antimicrobial therapy or prostaglandins within 7 days
4. Antihistamines within 14 days
5. Oral or topical glucocorticoids or ciclosporin within 21 days
6. Parenteral depot glucocorticoids within 56 days
7. Initiated or discontinued essential fatty acids within 56 days
8. Allergen-specific immunotherapy discontinued within 6 months or initiated within 12 months
9. Pregnancy or breeding activity
10. Concurrent condition that may deteriorate during the study

was allowed if necessary. Clinical assessments were performed on days 0, 28, 56 and 84 by investigators blinded to the treatment allocation. Each dog was examined by the same investigator throughout the trial to minimize interobserver variability. The investigators were all experienced referral dermatologists recognized by the European College of Veterinary Dermatology and/or the Royal College of Veterinary Surgeons. The total possible CADESI-03 scores range from 0 to 1260. The scores were used to define severity as follows: remission, 0–15; mild cAD, 16–59; moderate cAD, 60–119; severe cAD, ≥ 120 .¹⁹ If the CADESI-03 decreased to 59 or less (i.e. in remission or mild cAD as assessed by CADESI-03)¹⁹ at the re-examinations on days 28 or 56, the frequency of administration was reduced to every other day and then twice weekly. If the clinical signs subsequently worsened, the frequency of treatment was increased. Investigators performed a thorough clinical examination at each visit, recording and investigating any adverse events as appropriate.

Outcome measures

The outcome measures were the CADESI-03, pruritus and owner global evaluation scores (Table 2). Pruritus was assessed using a vertical 10 cm visual analog scale with grade descriptors (Figure 1).²¹ Owners were asked to mark the scale with a short horizontal line according to their perception of their dog's pruritus over the preceding 24 h. The pruritus score was the distance in millimetres from the bottom edge of the scale to their mark.

Data analysis

Dogs were withdrawn if they required treatment with a prohibited medication, experienced unacceptable discomfort or for poor compliance. Owners were free to withdraw their animals at any point. End-of-dosing assessments were recorded for intention-to-treat analyses using the last treatment value carried forward.

Table 2. Owners' global evaluation score

(1) Administration	
1	The treatment was very difficult to administer
2	The treatment was difficult to administer
3	The treatment was reasonably straightforward to administer
4	The treatment was easy to administer
5	The treatment was very easy to administer
(2) Tolerance	
1	The treatment was very poorly tolerated by my dog
2	The treatment was poorly tolerated by my dog
3	The treatment was reasonably tolerated by my dog
4	The treatment was well tolerated by my dog
5	The treatment was very well tolerated by my dog
(3) Efficacy	
1	The treatment did not work at all
2	The treatment was only marginally effective
3	The treatment partially resolved the skin problem
4	The treatment worked quite well
5	The treatment cleared up the skin problem

The owners were asked to tick the box that most closely resembled their impression of treatment at each revisit.

Extremely severe itching/almost continuous Itching doesn't stop whatever is happening, even in the consult room (needs to be physically restrained from itching) Severe itching/prolonged episodes Itching might occur at night (if observed), and also when eating, playing, exercising or being distracted Moderate itching/regular episodes Itching might occur at night (if observed, but NOT when eating, playing, exercising or being distracted) Mild itching/a bit more frequent Wouldn't itch when sleeping, eating, playing, exercising or being distracted Very mild itching/only occasional episodes The dog is slightly more itchy than it was when the skin problem first started Normal dog – I don't think that itching is a problem
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Figure 1. Visual analog scale with grade descriptors to evaluate pruritus. The owners were asked to mark the vertical line with a short horizontal line at the point they felt most closely matched their perception of their dog's pruritus over the preceding 24 h.

Two-way repeated-measures ANOVAs were used to evaluate the changes in CADESI-03 and pruritus scores between the treatment groups from day 0 to 84. Noninferiority was tested using Wilcoxon–Mann–Whitney tests with a simultaneous Wei–Lachin procedure.^{22–24} The benchmark values for equivalence were set at 0.36 and 0.64, which refer to a medium-sized difference, assuming a standardized difference of 0.5.²⁵ The proportions of dogs in each treatment group that could be maintained on daily, every-other-day or twice-weekly therapy were tested with the Mantel–Haenszel test. The time to first antimicrobial and/or glucocorticoid intervention in each group was described using a survival-type analysis. The proportions of dogs in each treatment group that required treatment with antimicrobials and/or systemic glucocorticoids were analysed with a Peto's log rank test. Fisher's exact tests or chi-squared tests were used to analyse differences in the proportions of dogs that achieved $\geq 50\%$ reductions in CADESI-03 and pruritus scores from baseline to

days 28, 56 and 84, and the frequency of treatment-related adverse events. Fisher's exact tests and Student's unpaired *t*-tests were used to analyse the demographic data. The level of statistical significance was set at $P < 0.05$ (two-sided).

Results

Demographic data

Twenty-five dogs from 15 breeds and crosses were enrolled in the HCA group, and 23 dogs from 10 breeds and crosses in the ciclosporin group. The range of breeds did not appear to differ between the groups, but the low numbers of each breed prevented statistical analysis. There were no significant differences in age (HCA, mean 5.3 years, range 1.5–12; and ciclosporin, mean 6.0 years, range 1.1–10; Student's unpaired *t*-test, $P = 0.33$), sex (HCA, 9 female, 14 male; and ciclosporin, 11 female, 10 male; Fisher's exact test, $P = 0.55$) or weight (HCA, mean 24.5 kg, range 4.2–68; and ciclosporin, mean 17.4 kg, range 3.8–46; Student's unpaired *t*-test, $P = 0.1$). Apart from flea control, none of the dogs received any concomitant therapy throughout the trial.

Intention-to-treat analyses

Eight dogs were prematurely withdrawn at the owner's request, on grounds of poor efficacy and/or for requiring treatment with a prohibited medication, as follows: HCA group, one dog between days 0 and 28, two dogs between days 28 and 56, and two dogs between days 56 and 84; and ciclosporin group, one dog between days 0 and 28, and two dogs between days 56 and 84 (Fisher's exact test, $P = 0.7$). On-treatment data were used for intention-to-treat analyses using the last treatment carried forward technique. One HCA-treated dog and two ciclosporin-treated dogs were excluded because of insufficient on-treatment data. There were no other significant protocol deviations in either group.

CADESI-03

The CADESI-03 scores in both treatment groups significantly decreased over time (two-way repeated-measures ANOVA, $P < 0.0001$; Figure 2). There was, however, no difference in response between the HCA- and ciclosporin-treated dogs ($P = 0.91$). There was also no significant time–treatment interaction ($P = 0.57$), indicating that treatment effects were consistent at each time point. Reductions of CADESI-03 scores following treatment with HCA and ciclosporin were nearly equivalent (0.47; lower and upper bounds 0.36–0.58), with no significant difference in treatment effect (Wilcoxon–Mann–Whitney/Wei–Lachin test, $P = 0.67$).

Similar proportions of the HCA- and ciclosporin-treated dogs achieved $\geq 50\%$ reductions in CADESI-03 compared with baseline at days 28, 56 and 84. There were no significant differences in response between the two treatment groups at any time point (Table 3).

On day 0, 21 of 23 HCA-treated dogs and 19 of 21 ciclosporin-treated dogs had moderate or severe cAD as assessed by the CADESI-03.¹⁹ By day 84, only three dogs in each group had moderate cAD and only two dogs in each group had severe cAD. Of the dogs that completed the trial (i.e. per-protocol rather than intention-to-treat

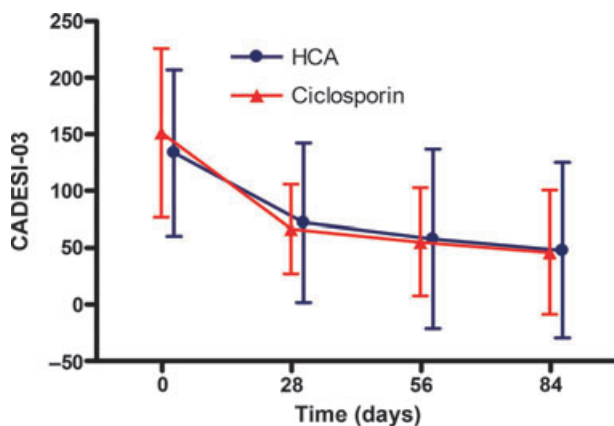


Figure 2. CADESI-03 scores in the hydrocortisone aceponate- ($n = 24$; HCA) and ciclosporin-treated dogs ($n = 21$; means $\pm$ SD).

Table 3. Proportions of the hydrocortisone aceponate- (HCA) and ciclosporin-treated dogs that achieved a $\geq 50\%$ reduction in CADESI-03 scores compared with baseline at each time point

	HCA ($n = 24$)	Ciclosporin ($n = 21$)	<i>P</i> -value
Day 28	14 (58.3%)	12 (57.1%)	0.76
Day 56	17 (70.8%)	17 (81%)	1.0
Day 84	18 (75%)	18 (86.7%)	0.72

data), only one HCA-treated dog and two ciclosporin-treated dogs had moderate cAD; the remainder had mild cAD or were in remission.

Pruritus

The pruritus scores in both the HCA- and the ciclosporin-treated dogs significantly decreased over time (two-way repeated-measures ANOVA, $P < 0.0001$), but there was no difference between the groups ($P = 0.52$; Figure 3). There was no significant time–treatment interaction ($P = 0.46$), suggesting that the treatment effects were consistent throughout the trial. The decreases in the pruritus scores were nearly equivalent (0.51; lower and upper bounds 0.35–0.68). There was no significant difference between the treatment effects ($P = 0.88$), although this finding could not be confirmed, because the lower and upper bounds were out of the predefined benchmarks for equality.

Similar proportions of the HCA- and ciclosporin-treated dogs achieved $\geq 50\%$ reductions in pruritus scores compared with baseline at days 28, 56 and 84. There were no significant differences in response between the two treatment groups at any time point (Table 4).

Owners' global evaluation scores

The owners' scores for efficacy (two-way repeated-measures ANOVA, $P = 0.008$), tolerance ($P = 0.02$) and ease of administration ($P = 0.01$) all significantly improved during the trial (Figure 4). There was, however, no significant difference between the HCA and ciclosporin treatment groups (efficacy, $P = 0.82$; tolerance, $P = 0.62$; and ease of administration, $P = 0.25$). There was no significant time–treatment interaction (efficacy, $P = 0.72$; tolerance, $P = 0.52$; and ease of administration, $P = 1.0$), indicating that the changes in scores were consistent at each time point.

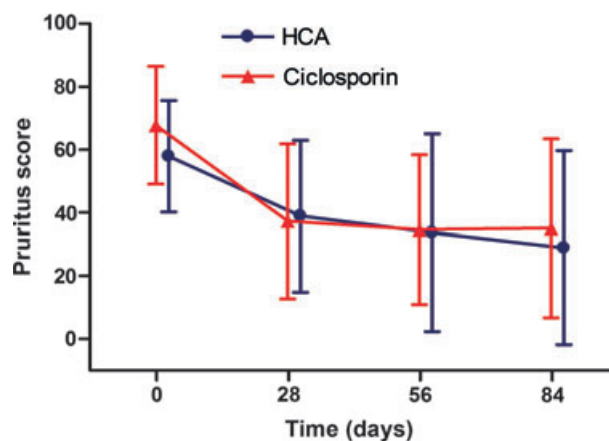


Figure 3. Pruritus scores in the hydrocortisone aceponate- ($n = 24$; HCA) and ciclosporin-treated dogs ($n = 21$; means $\pm$ SD).

Table 4. Proportions of the hydrocortisone aceponate- (HCA) and ciclosporin-treated dogs that achieved a $\geq 50\%$ reduction in pruritus scores compared with baseline at each time point

	HCA ($n = 24$)	Ciclosporin ($n = 21$)	<i>P</i> -value
Day 28	8 (33.3%)	8 (38.1%)	1.0
Day 56	15 (62.5%)	12 (57.1%)	1.0
Day 84	16 (66.6%)	12 (57.1%)	0.76

On day 84, the owners' scores for tolerance (0.49; lower to upper bound 0.34–0.64; $P = 1.0$) and ease of administration (0.46; lower to upper bound 0.30–0.62; $P = 0.75$) were close to equivalence, although this could not be confirmed because the lower bounds were out of the predefined benchmarks for equality. The score for efficacy favoured HCA (0.68; upper to lower bound 0.53–0.84; $P = 0.03$).

Frequency of treatment

The ability to reduce the frequency of dosing while maintaining the dogs in remission was similar in the HCA and ciclosporin treatment groups (Table 5). Overall, 38% of the HCA group and 48% of the ciclosporin group could be maintained on every-other-day treatment from day 28 to 56. From day 56 to 84, 54% of the HCA group and 57% of the ciclosporin group could be maintained on every-other-day or twice-weekly treatment. One dog in each group required an increase in dose frequency following worsening of their clinical signs at day 56. There were, however, no significant differences between the two treatment groups (Mantel–Haenszel test, $P = 0.85$).

Time to first intervention with antimicrobials or glucocorticoids

Two dogs in the HCA treatment group received a single course of topical antimicrobial/glucocorticoid treatment at day 56. One dog in the ciclosporin group received systemic antimicrobial treatment at day 28 and two dogs were treated at day 56. These dogs were excluded at the point of intervention and data carried forward for intention-to-treat analysis (see intention to treat analyses above). No other treatment interventions were reported in either group. There was no significant difference in the

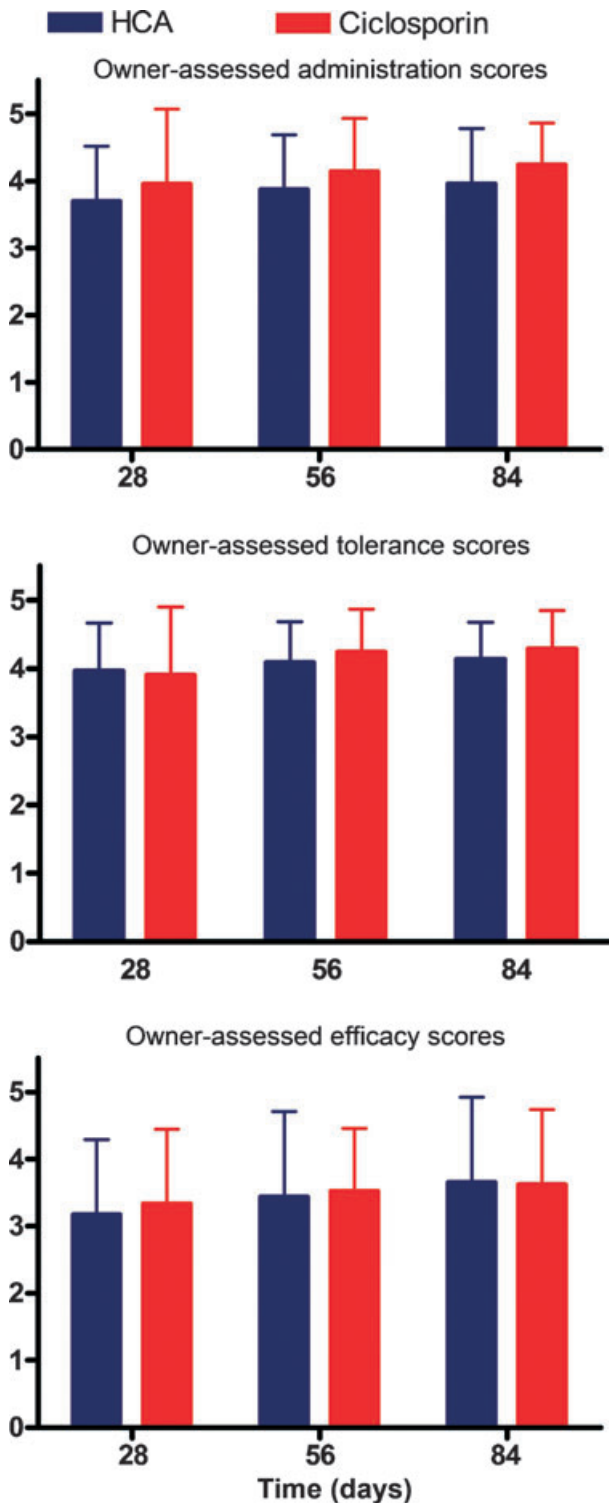


Figure 4. Owner assessments of ease of administration, tolerance and efficacy (0–5 scale; 0 = very poor and 5 = excellent) in the hydrocortisone aceponate ($n = 24$; HCA) and ciclosporin treatment groups ($n = 21$; mean $\pm$ SD).

frequency or time to intervention between the HCA- and ciclosporin-treated groups (Peto's log rank test, $P = 0.81$).

Adverse events

Both treatments were very well tolerated throughout the study. No adverse events attributable to the trial therapy

Table 5. Frequency of treatment with hydrocortisone aceponate (HCA) spray or ciclosporin required to maintain the treated dogs in remission

Frequency of treatment		HCA	Ciclosporin
Day 28–56	Once daily	15	11
	Every other day	9	10
	Twice weekly	0	0
Day 56–84	Once daily	11	9
	Every other day	3	2
	Twice weekly	10	10

were reported in the HCA group, although one dog required treatment for a traumatic limb injury on day 56. Seven adverse events possibly associated with ciclosporin therapy were seen in six dogs, as follows: day 28, vomiting (2), diarrhoea and vomiting (1), vomiting and anorexia (1) and diarrhoea (1); day 56, vomiting (1); and day 84, vomiting (1). The frequency of adverse events was significantly higher in the ciclosporin group (Fisher's exact test, $P = 0.008$). All the adverse events, however, were mild and short term, and did not require cessation of therapy or dose adjustment.

Discussion

This study shows that a topical 0.0584% HCA spray and systemic ciclosporin are both highly effective treatments for cAD. A majority of dogs in both groups achieved >50% reductions in clinical lesion and pruritus scores, the point conventionally used to denote a significant clinical improvement.⁴ Most dogs, furthermore, were classified as having mild cAD or were in clinical remission at the end of the trial. The response to treatment was very similar in both groups, with no significant differences in CADESI-03 scores, pruritus scores and the number of dogs that achieved >50% reductions in CADESI-03 and pruritus scores. There were, furthermore, no significant differences in the time to therapeutic intervention, or owner assessments of efficacy, tolerance and ease of administration. Noninferiority, however, could not be proved for all scores because the lower and upper bounds were out of the predefined benchmarks for equality due to the low power of the study design. This is probably because the study was designed to evaluate the comparative efficacy of HCA spray and ciclosporin in treating cAD. Equivalence studies to prove noninferiority of one intervention compared with another typically require very large numbers of dogs. The owner assessments of efficacy did reveal a small but significant superiority in the HCA group. The owner assessments, however, were not blinded and were therefore vulnerable to detection bias.

The clinical response was fairly rapid, with most of the improvement in clinical lesions and pruritus noted at day 28. Thereafter, it was possible to reduce the frequency of dosing while maintaining the clinical improvement in most dogs. The majority could be maintained on HCA spray or ciclosporin administered every other day or less often, although the longer term response was variable between dogs. This is similar to results published in other studies.^{5,6,14} Variation in the frequency of long-term medication needed to maintain remission of cAD may be due to the inherent severity of

condition, environment (e.g. allergen or irritant exposure), genotypic differences in response to drug therapy or with medication administration. These results are nevertheless encouraging, because monotherapy for cAD is not normally recommended.⁶ It is therefore possible that additional therapy, such as skin barrier care, allergen avoidance and allergen-specific immunotherapy, would permit less frequent treatment in more dogs. It is also possible to maintain remission in dogs treated with ciclosporin by continuing once-daily administration but reducing the dose.^{3,5,6} It is therefore possible that some of the dogs that required daily ciclosporin in this study could have been maintained on a lower dose. Daily dose reduction was not possible with the HCA spray, and therefore the study design only allowed adjustment of the frequency of treatment to allow comparison between the two treatment groups.

There were few cases of otitis or pyoderma in the HCA and ciclosporin treatment groups, although 26 of the 48 enrolled dogs had required topical or systemic antimicrobial and/or glucocorticoid treatment in the 3 months prior to the trial (data not shown). This indicates that these infections are secondary to changes in the cutaneous microenvironment that favour bacterial and/or *Malassezia* colonization and infection. Secondary infections are common in cAD, although virtually all infections appear to be associated with commensal organisms.²⁶ Control of inflammation therefore appears to be important in helping to prevent colonization and infection of the skin. Nonantimicrobial methods of controlling infection will be important in limiting the development of antimicrobial resistance. This apparent antimicrobial effect of anti-inflammatory medication therefore warrants further study.

It is interesting that the owner scores for ease of administration were similar in each group. The owners did not, therefore, appear to regard topical application of the HCA spray as more onerous than administration of the ciclosporin capsules. The results may, however, have been different in a cross-over study that would have allowed each owner to compare the treatment modalities directly. There was some variation in the scores, which probably represented a spectrum of easy and difficult dogs to medicate in both groups. The equivalence analysis revealed a nonsignificant superiority of ciclosporin at day 28, although no trends were seen at days 56 and 84. It is therefore possible that owners found the spray easier to administer with time, as they and their dogs became more used to it and/or treatment was required less often.

Both treatments were very well tolerated. There were no adverse events attributable to HCA treatment. Blood parameters or adrenal function were not measured, although no significant changes were seen following treatment for up to 70 days in a previous study.¹⁴ There was no clinical evidence of cutaneous atrophy or secondary infection, as noted in a previous study,¹⁴ although more recently cutaneous atrophy following 14 days treatment has been reported.¹⁶ Adverse events were significantly more frequent in the ciclosporin group, although this is of doubtful clinical significance because these were all minor gastrointestinal upsets that did not require specific therapy or changes to treatment. Gastrointestinal

disturbances associated with ciclosporin therapy are well recognized, but the majority are mild and transient.^{5–11} The results of this trial indicate that both HCA spray and ciclosporin have a better benefit:risk profile than other anti-inflammatory agents, such as antihistamines, aroflinone, misoprostol, traditional topical glucocorticoids and systemic glucocorticoids.^{6,27–32} This study, however, only followed dogs for a maximum of 84 days, and as cAD is usually a lifelong condition, good pharmacovigilance and longer term studies of safety are warranted.

Where possible, this study used reported and validated outcome measures. The CADESI-03 has high intra- and interobserver reliability, and is a relevant and reliable assessment of clinical severity.^{19,33} The lesion scores encompass features of acute and chronic inflammation, but only provide an indirect assessment of pruritus through excoriation. Direct pruritus scores, in contrast, have not been studied or validated to the same extent. Studies have questioned the reliability and repeatability of simple visual analog scale scores, and the combined visual analog scale with behavioural descriptors used in this study has been found to be superior.^{21,34} Nevertheless, while validated lesion and pruritus scores are useful for evaluating and comparing treatment, it is likely that quality of life is more important to owners and their dogs. It has been difficult to assess quality of life reliably, and studies have often reported global evaluation scores. These, however, can be misleading; for example, in an earlier trial of the HCA spray, some owners found the global score contradictory because they found the spray efficacious but difficult to apply.¹⁴ This study therefore divided the owners' evaluation into efficacy, ease of application and tolerance. Very recently, quality-of-life questionnaires have been developed and validated.^{35,36} Future studies of therapeutic interventions should evaluate these alongside clinical lesion and pruritus scores.

This study was carried out to good clinical practice standards.^{4,6} Rigorous inclusion and exclusion criteria were established before the trial to ensure an unambiguous diagnosis of cAD. Selection bias in breed, age, sex, weight and clinical severity was not apparent. Randomized treatment allocation was made according to a predetermined allocation code. Detection bias by the investigators was unlikely because they were blinded to treatment allocation, and treatment-related follow up was performed by a dispenser who did not participate in any outcome assessments. Detection bias by the owners, however, was highly likely with the single-blind design of the study. Performance bias was considered unlikely because there were no concomitant treatments apart from flea control. Attrition bias was present, with eight dogs withdrawn, although on-treatment data permitting intention-to-treat analysis was available for five of these dogs. Poor efficacy was an issue, although other reasons for withdrawal included withdrawal at the owners' request and/or treatment with prohibited medications. It is therefore possible that this biased towards a favourable response to treatment.

In conclusion, this study demonstrated that a 0.0584% HCA spray and ciclosporin were both highly efficacious and well tolerated in the treatment of cAD. There were no significant differences in clinical improvement or

owner assessment, although the study design lacked sufficient power to confirm noninferiority for all the outcome measures.

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Résumé Cette étude compare l'efficacité d'un spray à 0.0584% d'acéponate d'hydrocortisone (HCA) (Cortavance®; Virbac) et la ciclosporine (Atopica®; Novartis) dans la dermatite atopique canine (DAC) dans un essai contrôlé randomisé en simple aveugle. Les chiens ont reçu de l'HCA (2 sprays/100 cm²; $n = 24$) ou de la ciclosporine (5 mg/kg; $n = 21$). Le CADESI-03 (Canine Atopic Dermatitis Extent and Severity Index), le prurit (échelle visuelle avec description des grades) et les scores des propriétaires (échelle 5 points) ont été enregistrés tous les 28 jours pendant 84 jours. Les données d'ITT (Intention-to-treat) ont été analysées. Le CADESI-03 et le prurit ont significativement diminué avec le temps ($P < 0.0001$) mais il n'y avait aucune différence entre les groupes de traitement (respectivement $P = 0.91$ et $P = 0.52$). Des proportions identiques de chiens traités à l'HCA et à la ciclosporine ont montré une réduction du CADESI-03 et du prurit $\geq 50\%$ à J28 (CADESI-03 58.3% et 57.1%, $P = 0.76$; prurit 33.3% et 38.1%, $P = 1.0$), à J56 (CADESI-03 70.8% et 81.0%, $P = 1.0$; prurit 62.5% et 57.1%, $P = 1.0$) et à J84 (CADESI-03 75% et 85.7%, $P = 0.72$; prurit 65.2% et 57.1%, $P = 0.76$). Les scores de CADESI-03 et de prurit étaient presque équivalents (respectivement 0.47 et 0.51). A partir de J84, un jour sur deux ou deux fois par semaine, le traitement a été appliqué respectivement chez 13/24 chiens avec l'HCA et 12/21 chiens avec la ciclosporine ($P = 0.85$). Il n'y a eu aucune différence significative entre les scores d'efficacité ($P = 0.82$), de tolérance ($P = 0.62$) et de facilité d'administration ($P = 0.25$). Les scores de tolérance (0.49) et d'administration (0.46) étaient presque équivalents. Le score d'efficacité était meilleur pour l'HCA (0.68). Des effets indésirables modérés ont été notés dans 6/21 cas avec la ciclosporine et 0/24 cas avec l'HCA ($P = 0.008$). Cinq chiens recevant de l'HCA et trois chiens recevant de la ciclosporine ont été prématurément retirés de l'étude ($P = 0.7$). En conclusion, l'efficacité de l'HCA et de la ciclosporine est équivalente dans le traitement de la DAC pendant 84 jours.

Resumen Este estudio comparó la eficacia de un aerosol con un 0,0584% de aceponato de hidrocortisona (HCA) (Cortavance®; Virbac) y ciclosporina (Atopica®; Novartis) en el tratamiento de la dermatitis atópica canina (CAD) en un estudio controlado, con selección al azar y ciego simple. Los perros recibieron HCA (dos pulverizados/100 cm²; $n = 24$) o ciclosporina (5 mg/kg; $n = 21$). El índice de extensión y severidad de la dermatitis atópica (CADESI) - 03, el prurito (escala análoga visual con descripción del grado) y las puntuaciones de los propietarios (escala de 5 puntos) fueron registrados cada 28 días durante 84 días. Los datos fueron analizados según intención de tratamiento. CADESI-03 y el prurito disminuyeron perceptiblemente a lo largo del tiempo ($P < 0,0001$) pero no hubo ninguna diferencia entre los grupos de tratamiento ($P = 0,91$ y $P = 0,52$ respectivamente). Proporciones similares de animales tratados con HCA y ciclosporina alcanzaron una reducción $\geq 50\%$ en CADESI-03 y valores de prurito en el día 28 (CADESI-03 58,3% y 57,1%, $P = 0,76$; prurito 33,3% y 38,1%, $P = 1,0$), día 56 (CADESI-03 70,8% y 81,0%, $P = 1,0$; prurito 62,5% y 57,1%, $P = 1,0$) y día 84 (CADESI-03 75% y 85,7%, $P = 0,72$; prurito 65,2% y 57,1%, $P = 0,76$). CADESI-03 y los valores de prurito estuvieron cerca de ser equivalentes (0,47 y 0,51 respectivamente). Al llegar al día 84 se había llegado a tratamiento en días alternos o dos veces por semana en 13/24 perros para la HCA y 12/21 para la ciclosporina, respectivamente ($P = 0,85$). No había diferencias significativas en los valores de la eficacia ($P = 0,82$), tolerancia ($P = 0,62$) y facilidad de administración ($P = 0,25$). Los valores de tolerancia (0,49) y administración (0,46) estuvieron cerca de la equivalencia. Los valores para el tratamiento con HCA favorecieron la eficacia (0,68). Fenómenos adversos leves fueron observados en 6/21 de animales tratados con ciclosporina y 0/24 de animales tratados con HCA ($P = 0,008$). Cinco perros tratados con HCA y tres perros tratados con ciclosporina fueron retirados del estudio prematuramente ($P = 0,7$). En conclusión, HCA y ciclosporina fueron igualmente eficaces en el tratamiento de la CAD hasta los 84 días.

Zusammenfassung Diese Studie verglich die Wirksamkeit von 0,0584%igem Hydrocortison Aceponat (HCA) Spray (Cortavance®; Virbac) und Ciclosporin (Atopica®; Novartis) bei caniner atopischer Dermatitis (cAD) in einem einfachblinden randomisierten kontrollierten Versuch. Die Hunde erhielten HCA (zweimal gesprüht/100 cm²; $n = 24$) oder Ciclosporin (5 mg/kg; $n = 21$). Der Canine Atopische Dermatitis Extent und Severity Index (CADESI)-03, Juckreiz (visuelle-analoge-Skala mit Beschreibung der Grade) und Bewertungen der BesitzerInnen (5 Punkte Skala) wurden alle 28 bis 84 Tage festgehalten. Intention-to-treat Daten wurden analysiert. CADESI-03 und Juckreiz waren mit zunehmender Behandlungsdauer signifikant vermindert ($P < 0,0001$), aber es bestand kein Unterschied zwischen den Behandlungsgruppen ($P = 0,91$ bzw. $P = 0,52$). Bei einem ähnlichen Anteil der HCA und Ciclosporin behandelten Hunde erfolgte eine $\geq 50\%$ ige Reduktion des CADESI-03 und der Juckreizwerte am D28 (CADESI-03 58,3% und 57,1%, $P = 0,76$; Juckreiz 33,3% und 38,1%, $P = 1,0$), am D84 (CADESI-03 75% und 85,7%, $P = 0,72$; Juckreiz 65,2% und 57,1%, $P = 0,76$). CADESI-03 und Juckreizwerte waren fast equivalent (0,47 bzw. 0,51). Ab D28 konnte die Behandlung bei 13/24 mit HCA bzw. bei 12/21 mit Ciclosporin behandelten Hunde auf jeden zweiten Tag oder auf zweimal pro Woche ausgedehnt werden ($P = 0,85$). Es gab keine signifikanten Unterschiede bei den Werten für die Wirksamkeit ($P = 0,82$), Toleranz ($P = 0,62$) und Leichtigkeit der Verabreichung ($P = 0,25$). Die Werte für Toleranz (0,49) und Verabreichung (0,46) waren fast equivalent. Der Wert für die Wirksamkeit war bei HCA am besten (0,68). Milde Nebenwirkungen bestanden bei 6/21 mit Ciclosporin und bei 0/24 mit HCA behandelten Hunden ($P = 0,008$). Fünf mit HCA behandelte Hunde und drei mit Ciclosporin behandelte Hunde wurden frühzeitig aus der Studie genommen ($P = 0,7$). Zusammen-

fassend kann man sagen, dass sich HCA und Ciclosporin bei der Behandlung von cAD für eine Dauer von bis zu 84 Tagen als gleich wirksam erwiesen haben.

要約 この研究では 0.0584% ヒドロコルチゾンアセポン酸エステル(HCA)スプレー(Cortavance®; Virbac)とシクロスポリン(Atopica®; Novartis)の効果を犬アトピー性皮膚炎(cAD)で一重盲検ランダム化対照試験で比較した。犬には HCA (spray2 回/100 cm²; $n = 24$)、またはシクロスポリン(5 mg/kg; $n = 21$)を投与した。犬アトピー性皮膚炎範囲と重症度指数 (CADESI)-03、 痒痒 (程度の説明を加えたビジュアルアナログスケール) と飼主によるスコア (5 点スコア) を 28 日ごと 84 日間記録した。入症した全員のデータを解析した。CADESI-03 と痒痒は有意に経時的に減少したが ($P < 0.0001$)、治療群間には違いはなかった(それぞれ $P = 0.91$ と $P = 0.52$)。HCA とシクロスポリンで治療した犬の CADESI-03 と痒痒スコアが 50%以上減少した割合は 28 日目では (CADESI-03 58.3% と 57.1% ($P = 0.76$)、痒痒スコア 33.3% と 38.1% ($P = 1.0$), 56 日目では(CADESI-03 70.8% と 81.0%, ($P = 1.0$)、 痒痒 62.5% と 57.1% ($P = 1.0$) と 84 日目では (CADESI-03 75% と 85.7%, $P = 0.72$; 痒痒 65.2% と 57.1% ($P = 0.76$))であった。CADESI-03 と痒痒スコアはほとんど同等だった (それぞれ 0.47 と 0.51)。HCA 群の 13/24 頭とシクロスポリン群の 12/24 頭で、D84 までに隔日または週 2 回投与が行えた($P = 0.85$)。治療効果 ($P = 0.82$)、寛容度($P = 0.62$)、投与のしやすさ($P = 0.25$)のスコアはいずれにも有意差はなかった。寛容度(0.49)と投薬(0.46)のスコアはほぼ同等であった。治療効果のスコアは HCA が高い傾向にあった (0.68)。6/21 頭のシクロスポリンと 0/24 頭の HCA の犬で軽度の副作用がみられた($P = 0.008$)。試験途中で中止・脱落したのは HCA 群 5 頭とシクロスポリン群 3 頭であった($P = 0.7$)。結論として、cAD の治療において、HCA とシクロスポリンは投与 84 日までその効果が同等であることが証明された。