Efficacy of proactive long-term maintenance therapy of canine atopic dermatitis with 0.0584% hydrocortisone aceponate spray: a double-blind placebo controlled pilot study

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Efficacy of proactive long-term maintenance therapy of canine atopic dermatitis with 0.0584% hydrocortisone aceponate spray: a double-blind placebo controlled pilot study

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Background – Long-term remission between flares of canine atopic dermatitis (CAD) can be difficult to achieve. Therefore, additional strategic forms of treatment are needed in order to target flare prevention. The concept of proactive therapy is recommended in the European guidelines for the treatment of human atopic eczema.

Objectives – To evaluate the efficacy of a proactive treatment regimen with a 0.0584% hydrocortisone aceponate (HCA) spray for CAD.

Animals – Client-owned dogs with spontaneous atopic dermatitis (AD) (n = 41).

Methods – This pilot study was conducted as a randomised, placebo-controlled, double-blinded clinical trial with an end-point of treatment failure. Dogs were treated once daily to remission, then randomly assigned to receive either the HCA spray (n = 21) or a placebo (n = 20) spray on two consecutive days each week. All dogs were on appropriate flea control. No topical or systemic anti-inflammatory or antimicrobial agents were permitted. Intention-to-treat analysis was used.

Results – At Day 0, all the dogs were in remission or had mild AD based on their Canine Atopic Dermatitis Extent and Severity Index, version 3 (CADESI-03) scores. The time to relapse was significantly higher in the HCA group (median 115 d; range 31–260 d) compared to the placebo group (median 33 d; range 15–61 d) ($P < 0.0001$). No adverse events were attributable to the HCA spray. Four dogs were lost to follow-up and four were withdrawn after receiving prohibited medication.

Conclusions and clinical importance – These results indicate that proactive long-term therapy of CAD with an HCA spray administered on two consecutive days each week is effective and well-tolerated.

Introduction

Canine atopic dermatitis (CAD) is a common, highly pruritic disease characterized by a waxing and waning course with frequent flares of inflammation. Treatment of severe and chronic cases can be challenging, and CAD is often associated with diminished quality of life in dogs and an economic burden for their owners.[1,2]

There are several treatment options for acute flares and chronic disease, which are well described in the literature and have been summarized in guidelines from the then International Task Force on Canine Atopic Dermatitis [now the International Committee for Allergic Diseases in Animals (ICADA)].[3,4] Nevertheless, long-term remission between flares can be difficult to achieve. Therefore, additional strategic forms of treatment are needed in order to target flare prevention.

In humans, there is evidence that clinically normal, non-lesional atopic skin is, in fact, not 'normal'. Based on findings that the skin of patients with atopic dermatitis (AD) has impaired barrier function and subclinical inflammation, the traditional reactive approach to therapy has been challenged in recent years by the proactive therapy concept. The latter is defined as a combination of pre-determined, long-term, low-dose, anti-inflammatory treatment applied to previously affected areas of skin.[5–8] The first trial with intermittent topical steroid use was published as early as 1999.[9] Today the concept of proactive therapy is recommended in the European guidelines for treatment of human atopic eczema.[6,10] Similarly, apparently nonle-

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sional skin of atopic dogs exhibits barrier defects and inflammation.[11–13]

Hydrocortisone aceponate is a potent steroid with a low rate of percutaneous absorption and consequently a low potential for systemic toxicity.[14] A 0.0584% hydrocortisone aceponate (HCA) spray (Cortavance®, Virbac Animal Health; Carros, France) has been shown to be highly effective and well tolerated in CAD for up to 84 days,[3,15] and it is recommended for the management of acute flares and chronic AD.[4] However, these studies did not evaluate the long-term efficacy of HCA in preventing exacerbations of AD once in remission.

The goal of our study was to perform a placebo-controlled, double-blinded pilot study to evaluate the efficacy of long-term, proactive, intermittent treatment with HCA in CAD flare prevention.

Materials and methods

Study design

This was a randomized, double-blinded, placebo (vehicle)-controlled, parallel-grouped study. The primary objective was to evaluate the efficacy and safety of an HCA twice weekly maintenance regime in reducing the risk of relapse in CAD.

Subjects

Client-owned dogs with recurrent perennial AD were eligible for the study and were recruited during a flare. The clinical diagnosis of AD was made according to accepted criteria and after ruling out other causes of pruritus.[16] Briefly, there must have been a compatible history, clinical criteria strongly associated with the disease, exclusion of other pruritic skin diseases with no response to an 8-week (minimum) elimination diet trial consisting of either home-cooked single protein or commercial hydrolysed protein diet, an 8-week veterinarian-approved flea control regimen, and exclusion of sarcoptic mange by trial therapy and/or negative serology. At least one positive reaction to a perennial allergen on intradermal or serological testing was required for enrolment.

Exclusion criteria included any conditions for which topical corticosteroids were contraindicated, other dermatological conditions that might have prevented accurate assessment of AD and any concomitant medications that might have interfered with the study's outcome. Participating dogs were required to receive appropriate flea control throughout the trial. Essential fatty acids, allergen-specific immunotherapy (ASIT) and emollient shampoos were permitted if they had been used prior to the trial and the dog had stable disease. No topical or systemic anti-inflammatory (besides HCA) or antimicrobial agents were permitted during the trial.

Owners provided written informed consent for inclusion of their dogs in the study.

Trial protocol

Phase 1 (stabilization): 0.0584% HCA spray was applied to affected skin according to the manufacturer's recommendations (i.e. two pumps at 10 cm distance from the skin, per 100 cm^2 surface area) until remission. Remission was defined as a Canine Atopic Dermatitis Extent and Severity Index, version 3 (CADESI-03) score of 59 or less, corresponding to remission or mild CAD.[17] Full clinical assessments, including the CADESI-03 evaluations, were performed every 2 weeks during this stabilization phase.

Phase 2 (evaluation): the duration of clinical remission of AD was evaluated during use of 0.0584% HCA or a placebo spray, which were applied on two consecutive days each week (e.g. Saturday and Sunday) at the previously affected sites.

Experimental design

An unpredictable allocation sequence was generated using four groups (two placebo and two HCA) to reduce bias among owners and the investigator. Dogs with AD that fulfilled the admission criteria and completed Phase 1 were randomly allocated in Phase 2 to receive either 0.0584% HCA or placebo according to the sequence established before the trial. Assignment to a group was masked from the owners and investigator until the trial was completed. The HCA spray and the placebo were supplied in identical bottles. They were pre-packaged and labelled A, B, C or D. A single investigator assessed all of the treatment outcomes and was not involved in treatment allocation. A student or a nurse dispensed the bottles to the owners and maintained the corresponding records.

Participants were assessed every 2 weeks for the first 45 days of the trial, then monthly (or sooner in the case of relapse). The investigator performed a thorough clinical examination at each visit, recording and investigating any adverse events including cutaneous atrophy. The end-point (failure) was considered to be a CADESI-03 score of 60 or above, and/or otitis, pyoderma or pruritus requiring treatment with a prohibited medication (i.e. topical or systemic anti-inflammatory or antimicrobial treatment). Dogs were also withdrawn for poor compliance and owners were free to withdraw from the trial at any point. Elapsed time from Day 0 to the end-point was recorded. Upon failure, dogs were removed from the study and prescribed appropriate medications. After a pre-defined period of time (12 months) the study was concluded.

Custom-made journal forms were given to the owners to record treatment applications, unexpected occurrences or adverse effects. Regular telephone calls to the owners were made to obtain updates on the treatment plan and the dog's condition. At the end of the trial the owners were asked to return all bottles (empty or not) so that compliance could be assessed.

Data analysis

The primary end-point was the time to relapse of clinical signs during the maintenance phase. On-treatment data were used for intention-to-treat analysis using the last-observation-carried-forward technique for dogs that were withdrawn for poor compliance, at the owners' request, or lost to follow-up. The Kaplan–Meier method was used to estimate the distribution of time to relapse of AD.

Results

From the group initially enrolled ($n = 41$), four dogs were lost to follow-up. Three of these were from the HCA group; one died from an unrelated cause and the other two were excluded due to lack of compliance. In addition, one dog from the placebo group was excluded for non-compliance. Four dogs from the placebo group were prematurely withdrawn from Phase 2 due to administration of a prohibited medication.

There were no significant differences in clinical or demographic baseline values between the two groups (HCA and placebo) at the beginning of treatment. There were also no significant differences between dogs that received ASIT and/or emollient shampoos when compared to those that did not.

Kaplan–Meier survival analysis revealed that the median time to relapse was 115 d in the HCA group (range 31–260 d) and 33 in the placebo group (range 15–61 d; Figure 1). Medians between treatment groups differed significantly (two-tailed $P < 0.0001$). The risk for flare development under proactive HCA therapy was 3.5-fold lower than under placebo therapy. Fifty days after the beginning of Phase 2 more than 85% of the placebo group had relapsed in comparison to only two of the HCA group. Relapse rates in the HCA group were 60% at 100 d and 80% at 180 d. No adverse events attributable to HCA spray were noted.

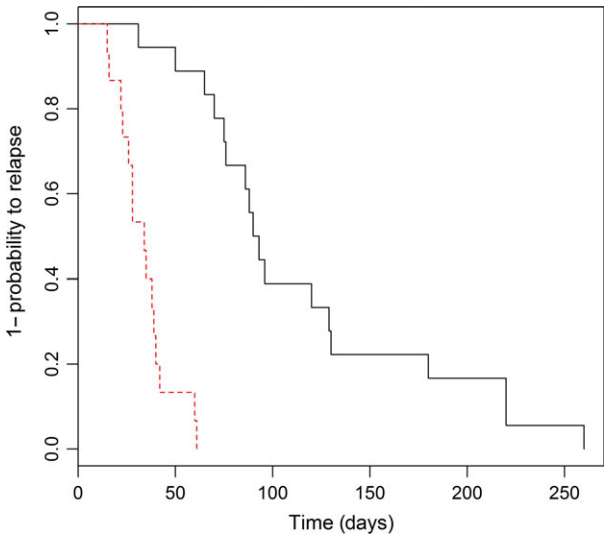

Figure 1. Kaplan–Meier survival analysis for comparing times to relapse in the therapy of canine atopic dermatitis: ---, placebo group; —, Cortavance (0.0584% hydrocortisone aceponate spray) group.

Discussion

Long-term therapy of CAD with HCA spray administered on two consecutive days each week was effective in reducing the risk of relapse and was well tolerated in this group of dogs. Our results show that proactive therapy in CAD can control residual disease with minimal anti-inflammatory drug use. To the best of the authors' knowledge, this is the first randomized, controlled clinical trial to examine longer term management of CAD with a proactive regimen using a topical glucocorticoid. The focus of the trial was on maintaining remission rather than on initial control of the clinical signs, and assessed the effect of treatment on the time to relapse, an important clinical outcome in this chronic, recurrent skin condition. This outcome may be beneficial in terms of safety, tolerance, quality of life and costs. Our results are in line with recent findings in human AD, where the concept of proactive therapy is recommended for the treatment of human atopic eczema.[6,10,18]

Textbooks and position papers on the treatment of CAD refer to topical glucocorticoid therapy for visible skin lesions. However, once there are no longer visible skin lesions, therapy is often tapered and discontinued. This treatment concept is now referred to in human medicine as 'reactive therapy'.[5] Although acute treatment flares can be managed successfully with this strategy, recurrence is the rule if no other forms of therapy are provided.

Proactive therapy begins with intensive topical anti-inflammatory therapy until lesions are in remission. However, the novel and pertinent aspect of such therapy is the subsequent long-term, low-dose, intermittent application of the anti-inflammatory agent to the previously affected skin.[19] Acceptance of this concept, even in human medicine, is new: the immunobiological background explanation was first published in 2009.[20] According to these authors the immunodermatological rationale to this approach is the ongoing epidermal barrier dysfunction, the residual inflammatory skin infiltrate and the persistent immunological abnormalities which are all present but clinically invisible.[20] Canine AD shares many clinical and immunological similarities with its human counterpart, including evidence of skin barrier dysfunction, persistent inflammation and immunological activation even in skin that macroscopically appears to be uninvolved.[11,13,21–25] Therefore, the underlying logic for the success and justification of the proactive approach is similar in human and canine AD.

As noted in earlier studies, the clinical response to HAC was quite rapid for the dogs that responded, where clinical remission was achieved within 1 month of initiating daily treatment.[15,26] Intermittent therapy maintained remission, although the longer term response was variable between dogs. This is similar to results published in other studies.[15,26] Variation in the frequency of long-term medication needed to maintain remission of AD may be due to the inherent severity of condition, environment (e.g. allergen or irritant exposure), and/or genotypic differences in response to drug therapy or with medication administration. These results are nevertheless encouraging, as monotherapy for CAD is not normally recommended.[4] There was concomitant treatment with ASIT and/or emollient shampoos in some dogs, but this did not appear to affect the results. However, it is possible that additional and better targeted therapies such as skin barrier care, allergen avoidance and ASIT would extend the duration of remission in more dogs.

The treatment regimens in this study were well tolerated. Skin biopsies or adrenocorticotropic hormone (ACTH)-stimulation tests were not performed, but a previous study did not find any changes in haematology, biochemistry or ACTH-stimulation tests in dogs treated once daily, every other day for up to 70 days.[27] There was no clinical evidence of cutaneous atrophy or secondary infection, as noted in a previous study,[26] although cutaneous atrophy following 14 days of treatment has been reported.[14] Canine AD is usually a lifelong condition and our study followed dogs for a maximum of 12 months. Therefore, pharmacovigilance and longer term studies of safety are warranted.

This study used a validated outcome measure (the CADESI-03) which has high intra- and interobserver reliability, and provides a relevant and reliable assessment of clinical severity.[17] The lesion scores encompass features of acute and chronic inflammation, but only provide an indirect assessment of pruritus through excoriation. Direct pruritus scores have not been studied or validated to the same extent, and although a combined Visual Analog Scale (VAS) scale with behavioural descriptors has been used in other studies with the HCA spray,[28] severity thresholds had not been established at the time of the study. It was therefore decided to not use specific pruritus scores as an end-point measure. However, when pruritus became severe enough to necessitate pharmacological intervention (in the opinion of either the owner or investigator), this was used as a study end-point.

Owner scores for ease of administration, tolerance and efficacy were not recorded, as the placebo was identical in form and administration to the active HCA spray and the end-point was relapse rather than efficacy. Previous

studies reported favourable owner scores for the HCA spray, albeit with some variation in ease of application.[15,26] These scores tended to improve with time, possibly because owners learned to apply the spray more effectively as they and their dogs adapted to it, and application was required less often. It has been difficult to reliably assess quality of life for dogs with AD, but quality of life questionnaires have been developed and validated subsequent to the initiation of this study.[1,2] Future studies of therapeutic interventions should evaluate these alongside other outcomes.

This study was carried out according to Good Clinical Practice (GCP) standards.[29] Rigorous inclusion and exclusion criteria were established before the trial to ensure an unambiguous diagnosis of AD. Selection bias in breed, age, sex, weight and clinical severity was not apparent. Randomised treatment allocation was made according to a predetermined allocation code. Detection bias by the investigators was unlikely as they were blinded to treatment allocation, and a dispenser who did not participate in any outcome assessments performed treatment-related follow-up. Ideally the bottles would have been sequentially numbered and each patient assigned their own number to further minimize any detection bias. However, the number of dogs, size, range and length of the study made this impractical. Performance bias was considered unlikely as concomitant treatments were predefined, stabilized before the trial, maintained during the trial, and were similar between the placebo and HCA groups. Attrition bias was potentially present, with eight dogs withdrawn from the two phases of the study; however, on-treatment data were available which permitted ITT analysis that reduces the risk of bias.

In conclusion, this study demonstrated that a 0.0584% HCA spray was efficacious and well tolerated in the proactive treatment of CAD. Proactive management to maintain remission should improve quality of life for dogs with AD and their owners. Further studies using the HCA spray and other products are required to determine whether this approach is as valid in CAD as in human AD.

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Résumé

Contexte – Une rémission à long terme entre les crises de dermatite atopique canine (DAC) peut être difficile à obtenir. Ainsi, de nouvelles stratégies thérapeutiques sont nécessaires afin de cibler et de prévenir les crises. Le concept de thérapie proactive est recommandé en Europe pour le traitement de l'eczéma atopique de l'homme.

Objectifs – Evaluer l'efficacité d'un traitement proactif pour la DAC avec un spray à 0.0584% d'acéponate d'hydrocortisone (HCA).

Sujets – Les chiens de propriétaires atteints de dermatite atopique spontanée (AD) (n = 41).

Méthodes – Cette étude pilote a été menée en tant qu'essai clinique en double aveugle, contrôlée contre placebo et randomisée avec l'échec de traitement en critère d'évaluation. Les chiens ont été traité une fois par jour jusqu'à rémission puis assignés au hasard pour recevoir soit le spray HCA (n=21) soit le spray placebo (n=20) deux jours consécutifs chaque semaine. Tous les chiens recevaient un traitement antipuce correct. Aucun agent antimicrobien ou anti-inflammatoire topique ou systémique n'était autorisé. Une analyse en ITT a été utilisée.

Résultats – A jour 0, tous les chiens étaient en rémission ou présentait une AD modérée basée sur leurs scores de CADESI-03 (Canine Atopic Dermatitis Extent and Severity Index, version 3). Le temps de rechute était significativement plus élevé dans le groupe HCA (médiane 115 d; écart 31–260 d) comparé au groupe placebo (médiane 33 d; écart 15–61 d) ($P < 0.0001$). Aucun effet secondaire n'était attribuable au spray HCA. Quatre chiens ont été perdus de vue et quatre ont été retirés de l'étude ayant reçu un traitement non-autorisé.

Conclusions en importance clinique – Ces résultats indiquent qu'un traitement proactif sur le long terme de la DAC avec un spray HCA administré deux jours consécutifs chaque semaine est efficace et bien toléré.

Resumen

Introducción – la remisión a largo plazo entre ataques de dermatitis atópica canina (CAD) puede ser difícil de conseguir. Por lo tanto, se necesitan estrategias adicionales de tratamiento para prevenir la aparición de esos ataques. El concepto de terapia proactiva está recomendado en los parámetros europeos para el tratamiento del eccema atópico humano.

Objetivos – evaluar la eficacia de un régimen de tratamiento proactivo con un espray de 0,0584% de aceponato de hidrocortisona (HCA) para CAD.

Animales – perros de propietarios privados con dermatitis atópica espontánea (AD) (n = 41).

Métodos – este estudio piloto fue conducido como un estudio clínico al azar, controlado por placebo y doble ciego con un punto final de fallo del tratamiento. Los perros pueden fueron tratados una vez al día hasta la remisión, y después asignados al azar para recibir bien el espray de HCA (n = 21) o un espray placebo (n = 20) en dos días consecutivos cada semana. Todos los perros estaban con un control apropiado frente a las pulgas. No se permitieron agentes tópicos o sistémicos antiinflamatorios ni antimicrobianos. Se utilizó un análisis de intención de tratar.

Resultados – en el día cero, todos los perros estaban en remisión o tenían dermatitis atópica leve basado en su índice de extensión y severidad de dermatitis atópica canina, versión tres (CADESI-03). El tiempo hasta la reaparición fue significativamente mayor en el grupo tratado con HCA (media 115 días; rango 31 a 260 días, comparado con el grupo placebo (media 33 días, rango de 15-61 días) ($P <0,0001$). No se observaron efectos adversos atribuidos al espray de HCA. Cuatro perros se perdieron al seguimiento y cuatro perros fueron desechados del estudio tras recibir medicación prohibida.

Conclusión e importancia clínica – estos resultados indican que la terapia proactiva a largo plazo de un espray de HCA administraba en dos días consecutivos cada semana es efectiva y bien tolerada.

Zusammenfassung

Hintergrund – Es kann zwischen den Schüben der atopischen Dermatitis des Hundes (CAD)schwierig sein eine Langzeitremission zu erzielen. Daher sind zusätzliche Behandlungsstrategien nötig, um gezielt Schübe zu verhindern. Das Konzept einer proaktiven Therapie wird in den Europäischen Richtlinien zur Behandlung des atopischen Ekzems beim Menschen empfohlen.

Ziele – Eine Evaluierung der Wirksamkeit einer proaktiven Behandlung mit einem 0,05845%igem Hydrocortison Aceponate (HCA) Spray bei CAD.

Tiere – Hunde in Privatbesitz mit spontaner atopischer Dermatitis (AD)(n=41).

Methoden – Diese Pilotstudie wurde als randomisierte, Plazebo-kontrollierte, doppelblinde klinische Studie mit Versagen in der Endpunktstudie durchgeführt. Die Hunde wurden bis zur Remission einmal täglich behandelt, danach wurden sie zufällig eingeteilt, um entweder HCA Spray (n=21) oder Plazebo (n=20) Spray an zwei aufeinanderfolgenden Tagen jeder Woche zu erhalten. Alle Hunde hatten eine geeignete Flohprophylaxe. Es waren keine topischen oder systemischen Entzündungshemmer oder Antibiotika erlaubt. Es wurde die Intention-to-treat Analyse verwendet.
Ergebnisse – Am Tag 0 befanden sich alle Hunde in Remission oder zeigten eine milde AD nach dem Canine Atopic Dermatitis Extent and Severity Index, Version 3 (CADESI-03). Die Zeit bis zur Wiederkehr von Symptomen war in der HCA Gruppe signifikant länger (Median 115d; Spannweite 31-260d) im Vergleich zur Plazebogruppe (Median 33d; Spannweite 15-61d)(P<0,0001). Bei der Verwendung des HCA Sprays wurden keine Nebenwirkungen beobachtet. Bei vier Hunden gab es keinen Follow-up und vier wurden aus der Studie genommen, nachdem sie eine unerlaubte Medikation bekommen hatten.
Schlussfolgerungen und klinische Bedeutung – Diese Ergebnisse zeigten, dass die proaktive Langzeittherapie bei CAD mit HCA Spray – verabreicht an zwei aufeinanderfolgenden Tagen pro Woche effektiv ist und gut toleriert wird.

要約
背景 — イヌアトピー性皮膚炎(CAD)の炎症の長期的な寛解を得ることは困難となりえる。それゆえに、追加の治療の戦略的方法が増悪の予防のために必要である。積極的な治療の概念が、ヨーロッパのヒトのアトピー性皮膚炎の治療のガイドラインでは奨励されている。
目的 — CADのための0.0584%ヒドロコルチゾールアセポネート(HCA)スプレーを用いた、積極的な治療方法の効果を評価すること。
供与動物 — 自然発症性アトピー性皮膚炎(AD)の飼い犬(n=41)
方法 — この試験的研究は、治療の失敗を終点としたランダム化二重盲検プラセボ比較試験として実施した。イヌを寛解まで1日1回治療し、その後、無作為に1週間毎に連続した2日、HCAスプレー(n=21)あるいはプラセボ(n=20)スプレーの塗布のいずれかに割り当てた。すべてのイヌに適切なノミ予防を行った。外用剤や全身投与の抗炎症剤や抗菌物質はいずれも禁止された。包括解析を解析に使用した。
結果 — 0日目に、すべてのイヌは寛解状態あるいは、Canine Atopic Dermatitis Extent and Severity Index、バージョン3(CADESI-03)スコアを基に評価した軽度のADであった。再発までの期間はプラセボ対照群(平均33日; 範囲15–61日)と比較し、HCA群(平均115日; 範囲31–260日)で有意に長かった(P < 0.0001)。HCAスプレーに起因した有害事象は報告されなかった。4頭が追跡不可能になり、4頭が禁止された薬剤投与後に脱落となった。
結論および臨床的な重要性 — これらの結果は、HCAスプレーを週に連続した2日間塗布する積極的なCADの長期的治療が、効果的であり、良好な耐容性を示すことを示唆している。

摘要
背景 — 犬异位性皮炎(CAD)很难做到长时间症状缓解。但是为了预防发病,也需要其他治疗形式。欧洲人异位性湿疹治疗指南提出前瞻性治疗概念。
目的 — 使用0.0584%氢化可的松醋丙酯(HCA)喷雾治疗CAD,评估此前瞻性治疗方法效果。
动物 — 患自发性异位性皮炎(AD) (n = 41)家养犬。
方法 — 初步研究使用随机、安慰剂对照、双盲临床实验,并以治疗失败为终点。犬每日治疗直至缓解期,然后随机给予HCA喷雾(n = 21)或安慰剂喷雾(n = 20),每周连续两天使用。所有犬均需适当的跳蚤控制。期间禁用局部或全身性抗炎药或抗菌剂。使用意向处理分析法。
结果 — 第0天,依据犬异位性皮炎程度和严重指数第3版(CADESI-03)评估,所有犬均处于缓解期或轻度AD。HCA组(中值115 天; 范围 31–260 天)复发时间明显长于安慰剂对照组(中值33 天; 范围15–61 d) (P < 0.0001). HCA喷雾组无不良反应。4只犬未能跟踪随访,4只犬未遵守禁止使用药物约定。
总结和临床意义 — 结论表明,每周连续2天使用HCA喷雾,长期前瞻性治疗CAD有效且耐受良好。