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Comparison of various treatment options for canine atopic dermatitis: a blinded, randomized, controlled study in a colony of research atopic beagle dogs

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Background – No study has directly compared the various treatment options for canine atopic dermatitis and their effects on skin barrier.

Hypothesis/Objectives – To compare prednisone, oclacitinib, ciclosporin and lokivetmab treatment of atopic dermatitis.

Animals – Nineteen atopic beagle dogs.

Methods and materials – Controlled, blinded study. Dogs were challenged with allergen twice weekly and randomized to oclacitinib, ciclosporin, lokivetmab, prednisone or no treatment for four weeks. Dermatitis and pruritus were assessed at baseline and after each challenge. Transepidermal water loss (TEWL) and hydration were measured at baseline, Day (D)14 and D28 (pinnae, axilla, groin). Area under the curve (AUC) was calculated for Canine Atopic Dermatitis Extent and Severity Index, 3rd iteration (CADESI-03), pruritus, TEWL and hydration. For CADESI, the AUC of the first two weeks was compared to that of the last two weeks.

Results – For CADESI, restricted maximum-likelihood ANOVA showed effect of time (P = 0034) and group x time interaction (P = 0.0169). In the first two weeks, prednisone and oclacitinib were significantly lower than controls (P = 0.019 and P = 0.015, respectively). Lokivetmab prevented flares. Due to variability, no significance differences in pruritus were observed among groups. The TEWL increased with time in controls (P = 0.0237) and ciclosporin (P = 0.04, axilla, D28 versus D0) but not in the oclacitinib and lokivetmab groups. CADESI-03 correlated with TEWL (P = 0.0043) and pruritus (P = 0.0283). Hydration did not correlate with any parameters. Hydration decreased in controls and prednisone group (axilla, D14 versus D0, P = 0.004 and P = 0.027, respectively). AUC for hydration, over time, was higher for lokivetmab and oclacitinib than controls (P = 0.014 and P = 0.04, respectively).

Conclusions and clinical importance – Lokivetmab prevented flares when given before challenge. Oclacitinib and lokivetmab have some positive effects on skin barrier parameters.

Introduction

Several treatments are available for canine atopic dermatitis (cAD). A few studies have compared efficacy of treatments, typically comparing two options at a time,[1-3] but never comparing multiple treatments concurrently in a controlled environment. Each option has strengths and weaknesses and it is useful to know how these treatments compare to each other, particularly in a controlled setting where allergen stimulation and diet are standardized.

A colony of atopic beagle dogs has been validated as model for spontaneously occurring cAD.[4] These dogs are easily sensitized percutaneously to allergens possibly due to skin barrier abnormalities;[5,6] they flare with dermatitis when exposed to allergen epicutaneously. These dogs are known to respond to commonly used treatments such as prednisone.[7]

Several studies have described skin barrier dysfunction in cAD. Although it is still unclear whether primary skin barrier defects exist in atopic dogs, it is known that skin barrier is aggravated by inflammation.[8] It is believed that skin barrier should improve when inflammation and/or pruritus are controlled although specific evidence is still lacking. Thus, it is helpful for clinicians to know if any of the available systemic treatments have beneficial effects on skin barrier parameters. We are still limited in making a reliable assessment of skin barrier parameters and no perfect methodology has been identified.[9] The most commonly assessed parameters are transepidermal water loss (TEWL) and hydration. In human patients with AD, TEWL is increased and hydration is decreased.[10] In atopic dogs, TEWL has been reported to be increased[11] whereas decreased hydration has not, as yet, been

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confirmed.[9] Despite the limitations of these methodologies and our incomplete knowledge of the relevance of hydration in cAD, it would be interesting to know if any of the available systemic treatments affects these parameters.

Thus, the aims of this prospective, blinded, controlled study were two-fold. The first aim was to concurrently evaluate the clinical efficacy of oral prednisone, oclacitinib, ciclosporin and injectable lokivetmab on severity of dermatitis and pruritus using a colony of atopic beagle dogs. In this colony, flares can be triggered by allergen exposure and camera recording of pruritus is possible. The second aim was to evaluate if any of these systemic treatments had measurable effects on TEWL and hydration.

Methods and materials

Animals and treatments

All procedures were approved by the Institutional Animal Care and Use Committee, College of Veterinary Medicine, University of Florida. Nineteen 8-year-old atopic beagle dogs (nine intact females, nine intact males, one neutered male) maintained in a research facility, which are sensitized to *Dermatophagoides farinae* were challenged with allergen twice weekly and allocated to receive either oclacitinib (Apoquel®, Zoetis; Kalamazoo, MI, USA) orally at a dose of 0.5 mg/kg twice daily for two weeks then once daily for two weeks, or ciclosporin (Atopica®, Elanco; Greenfield, IN, USA) p.o. at 5 mg/kg once daily for 28 days, lokivetmab (Cytopoint®, Zoetis) given once subcutaneously at 2 mg/kg on the first day of allergen challenge, or prednisone (Teva Pharmaceuticals; Shawnee, KS, USA) p.o. at a dose of 0.5 mg/kg twice daily for two weeks, then 0.5 mg/kg once daily for one week, then 0.5 mg/kg once every 48 h for one week. A control group received no treatment. Allergen challenge was achieved by application of 1.6 mL of a 16.5 mg/mL *D. farinae* solution (Stallergenes Greer; Lenoir, NC, USA) epicutaneously to the inguinal area twice weekly (see Figure 1 for timeline) for a total of eight challenges without any prior shaving or tape stripping.

Dogs were housed in pairs in a research facility where runs were cleaned daily and no toys that could trap dust were allowed. Dogs were fed the same diet (Hill's Science Diet®, Chicken, small bites, Hill's Pet Nutrition, Inc.; Topeka, KS, USA with no change for six months before the study. Dogs were monitored throughout the study for evidence of adverse effects.

Clinical assessment of dermatitis

All clinical assessments were done by the same investigator who was unaware of treatment allocation. Dermatitis was evaluated using as validated scoring system the Canine Atopic Dermatitis and Extent Severity Index, 3rd iteration (CADESI-03).[12] Dogs were scored at various time points (Figure 1). These times were baseline [before any allergen exposure, Day (D)0], twice daily on the days of challenge (in the morning before allergen exposure and 6 h after) and the day following challenge (24 h post-challenge).

Clinical assessment of pruritus

Camera recordings were taken at baseline (D0) and on the first allergen challenge of each week of the study (D2, D9, D16 and D23), 4 h after allergen exposure). Pruritus was assessed by two people who were unaware of treatment allocation. Two scoring systems for pruritus were based on 30-min video recording using GoPro cameras (GoPro; San Mateo, CA, USA).

The first scoring was quantitative using the BORIS (Behavioral Observation Research Interactive Software) software (http://www.boris.unito.it/). This program allows computer-based review of recorded videos. BORIS was used to score the duration (s) of licking, biting and scratching. Videos were played in the software and when the dog performed an action of interest (e.g. licking, biting or scratching) a key was pressed by the observer. For biting or scratching, the observer pressed a key which indicated the start of the behaviour and pressed again to indicate the stop. For licking, each lick was indicated by a key press. These data were exported into an excel spreadsheet.

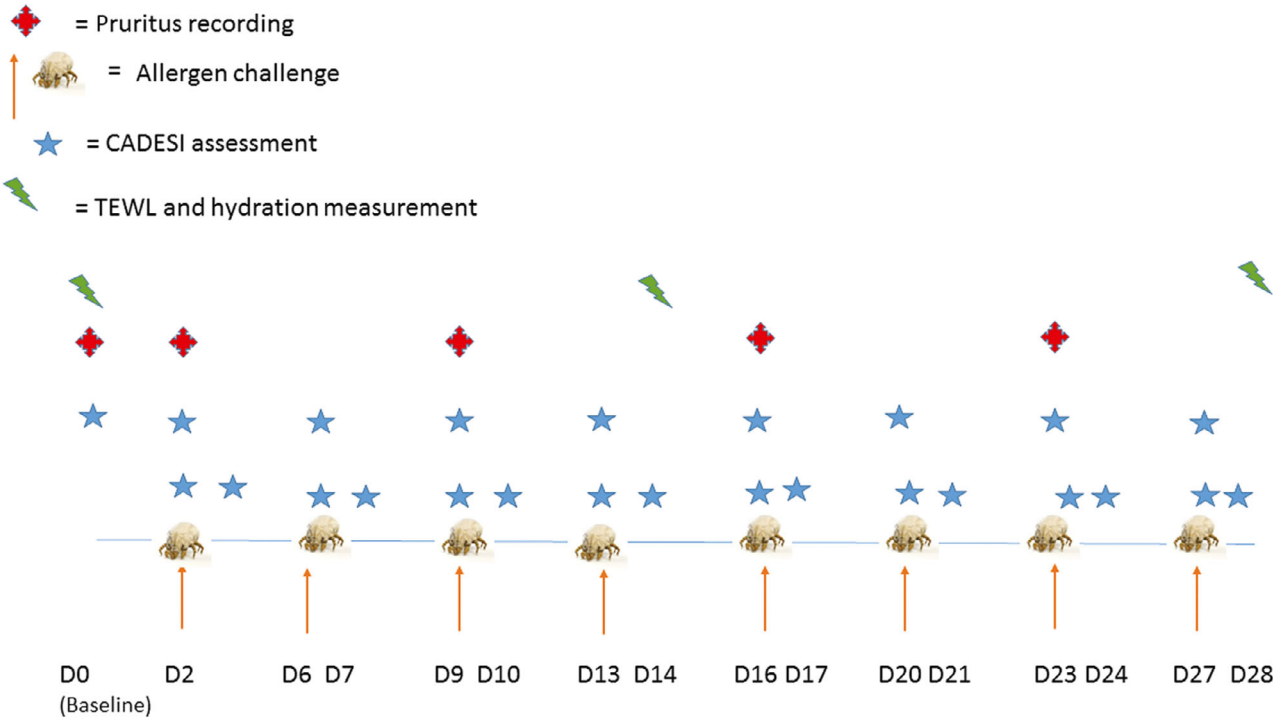

Figure 1. Timeline of the study showing when dogs were challenged with allergen and evaluated.
Allergen exposure was done twice weekly and CADESI was done before exposure, 6 h and 24 h after each exposure. Pruritus assessment was done at baseline and 4 h after each allergen exposure. Transepidermal water loss (TEWL) and hydration were measured at baseline, and every two weeks for two more times. Measurements were taken 24 h after allergen exposure.

The second scoring was a subjective global score called Pruritus Global Score using the Pruritus Visual Analog Scale (PVAS). This validated scoring system assigned a number ranging from 0 to 10 where higher numbers mean the most severe pruritus.[13] The number 0 was described as "no itching is observed" whereas 10 was described as "severe itching, manifested as interruption of eating, playing or resting in order to itch". Using this system, the same evaluators that reviewed the recordings placed a mark on a 10 cm scale as a subjective overall global assessment of their perception of the severity of the pruritus for each dog.

Assessment of skin barrier function

Skin barrier parameters were assessed every two weeks, on D0 (baseline, before allergen exposure), D14 and D28 (24 h post-allergen exposure). Parameters measured included TEWL and hydration.

TEWL. TEWL was measured using a closed chamer device (VapoMeter®, Delfin Technologies Ltd; Kuopio, Finland) at ambient temperature (20–26°C). Dogs were acclimatized for 30 min before TEWL measurements. All readings were collected in triplicate and means were used for statistical analysis. Three unclipped areas were evaluated: concave surface of pinnae, axilla and inguinal areas. These sites were selected because they are commonly affected in cAD, and a significant difference in TEWL between atopic and normal beagles had been reported for these areas.[5] Measurements were expressed as evaporation rate ($g/m^2/h$). Area under the curve (AUC) for TEWL was calculated and used for statistical analysis.[14]

Hydration. Hydration was measured using a Corneometer®, CM825® (Courage + Khazaka electronic GmbH; Cologne, Germany). Measurements were obtained by placing the probes perpendicular to the skin for 10 s with measurements obtained once per second. Values were expressed in micro siemens (μS), as conductance units.

Statistical analysis

The AUC was calculated for each dog and adjusted to baseline. For CADESI-03 scores, the four week period was divided into two periods of two weeks. This was done because treatment administration included a loading period (first two weeks) and a maintenance period (last two weeks) for some drugs (e.g. prednisone and oclacitinib). The first two weeks were referred as "T1 or Acute phase" and the final two weeks were referred to as "T2 or Chronic phase".

We used a mixed-model restricted maximum-likelihood 5-Group x 2-Time ANOVA (REML-ANOVA) with a between-subjects factor of Group (Control, Ciclosporin, Lokivetmab, Oclacitinib, Prednisone) and within-subject factor of Time (T1-Acute, T2-Chronic). AUC was calculated for TEWL and hydration for each site. The Kruskal–Wallis test was used to determine any difference between groups. Friedman's test was used to investigate an effect of time. The statistical software used was SAS System for Windows v9.0 (SAS Institute; Cary, NC USA). Statistical comparisons were considered to be significant when $P < 0.05$.

Results

CADESI

Means and standard deviations (SD) of the CADESI scores for all time points and all groups are presented in Figure 2. Large variability was observed with a typical increase of scores after allergen exposure.

REML-ANOVA yielded a significant main effect of time ($F_{1,14} = 12.41$, $P = 0.0034$), showing that AUC was greater at T2 than T1, and a significant group x time interaction ($F_{4,14} = 4.36$, $P = 0.0169$). Group x time interaction was driven largely by prednisone and oclacitinib groups, in which AUC/CADESI-03 increased in T2 compared to T1. The effect of group approached significance ($F_{4,14} = 2.754$, $P = 0.0616$). Prednisone and oclacitinib groups were significantly lower than controls during T1 ($P = 0.019$ and $P = 0.015$, respectively). Figure S1 shows CADESI/AUC for the various groups.

At D28, control dogs had evidence of severe dermatitis with erythema, excoriations and papules, whereas the lokivetmab and oclacitinib dogs had mild to no erythema. Ciclosporin-treated dogs showed evidence of dermatitis (Figure 3).

Pruritus

Large variability in pruritus was seen. The mean global score for pruritus (PVAS) and SD for the various groups are presented in Figure S2. Means and SD of pruritus [duration (s) of scratching during a 30-min recording] are presented in Figure S3. When AUC for pruritic seconds was calculated for T1 and T2 (Figure S4), due to the large variability, no statistically significant difference was detectable.

Skin barrier parameters

TEWL. On D0 there was no difference between groups for any site (Figure 4). On D14, Kruskal–Wallis comparison found significant difference between groups ($P = 0.03$) for the inguinal site and Dunn's Multiple Comparison test found that the ciclosporin group had significantly higher TEWL than prednisone-treated dogs ($P = 0.0283$). On D28, Kruskal–Wallis comparison revealed significant differences between groups ($P = 0.03$), with controls having higher TEWL than prednisone and lokivetmab in pinnae and axillary areas ($P = 0.02$ and $P = 0.031$, respectively).

An effect of time for TEWL was noted in the prednisone-treated dogs (Friedman's test, $P = 0.004$), with an increase from D14 to D28, in axillary and inguinal areas ($P = 0.0400$ and $P = 0.014$, respectively).

An effect of time for TEWL was detected in ciclosporin-treated dogs for the axillae (Friedman's test, $P = 0.041$) with a significant increase from baseline (Dunn's Multiple Comparison test D0 versus D28, $P = 0.04$). No effect of time was seen for TEWL in lokivetmab- and oclacitinib treated dogs for any of the sites. An effect of time was seen on TEWL in the controls, with increased TEWL in the axillae (D0 versus D28, $P = 0.0237$).

When AUC was calculated by body site, for all groups, Kruskal–Wallis detected a difference between groups only for axillae ($P = 0.040$), with ciclosporin-treated dogs having higher values than prednisone-treated dogs ($P = 0.035$). When AUC was compared specifically between active treatments and controls, prednisone-treated dogs had significantly lower AUC ($P = 0.022$) in the axillae and ciclosporin-treated dogs had lower AUC in the pinnae ($P = 0.044$) than the control group.

Hydration. Compared to D0, controls and prednisone had decreased hydration in the axillae on D14 ($P = 0.004$ and $P = 0.027$, respectively); lokivetmab decreased hydration on D28 (pinnae, $P = 0.027$). When AUC for hydration values was calculated for all sites over time, values for lokivetmab- and oclacitinib-treated dogs were significantly greater and presumed to be more hydrated than controls ($P = 0.014$ and $P = 0.04$, respectively).

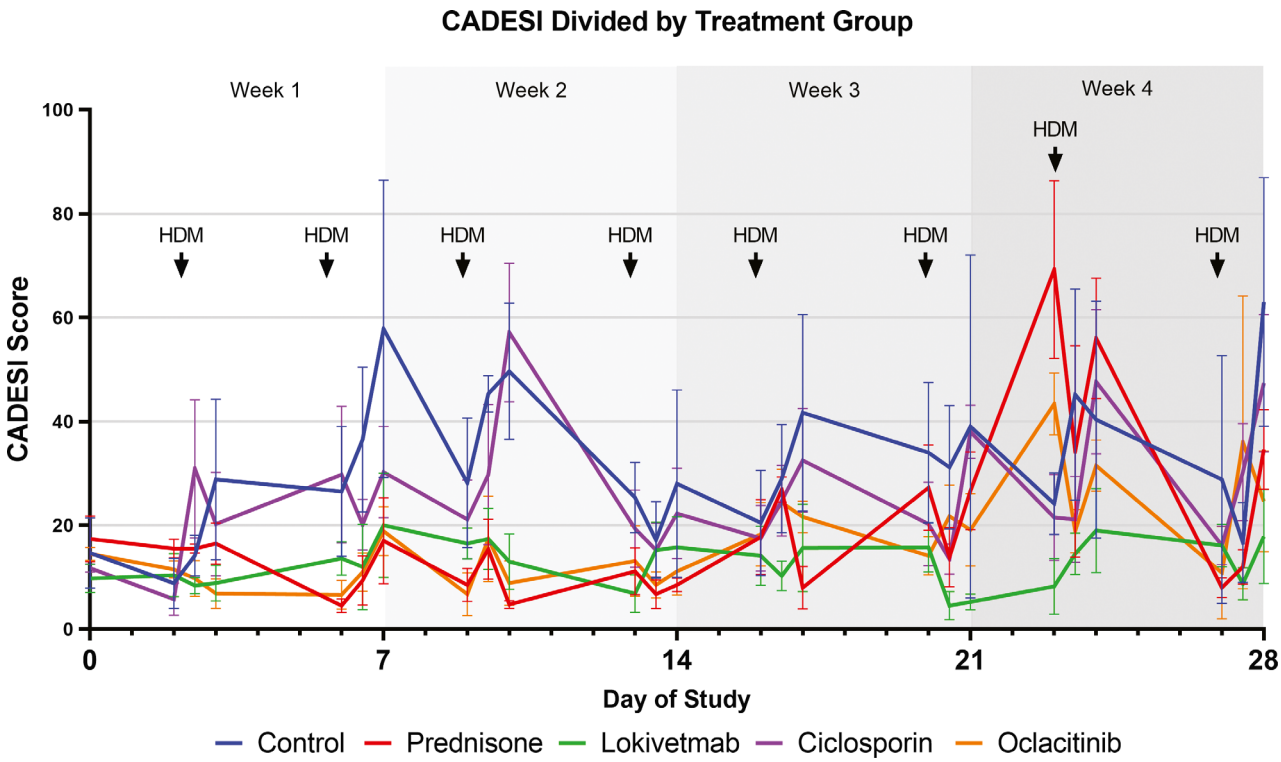

Figure 2. Means and standard deviations (SD) of all groups at all evaluation times.
The vertical red lines indicate when a change of regimen was done for the prednisone group. Prednisone was given twice daily for the first two weeks, once daily in Week 3 and every other day in Week 4.

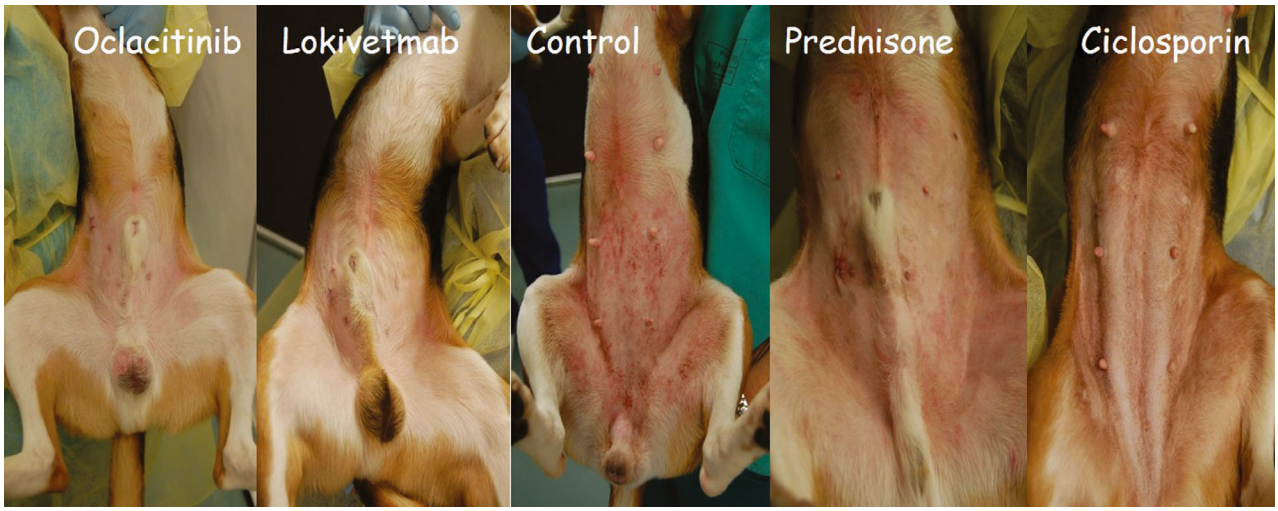

Figure 3. Composite showing pictures of a representative dog for each group on Day 28.
From left to right, there is a dog from the oclacitinib, lokivetmab, control, prednisone and ciclosporin groups. Control dogs had noticeable erythema, papules and excoriations, whereas dogs in the lokivetmab and oclacitinib groups had very mild to no erythema.

Correlations between skin barrier parameters and clinical parameters

CADESI correlated with TEWL ($r = 0.21$; $P = 0.0043$) and Pruritus Global Score or PVAS ($r = 0.22$; $P = 0.028$) (Figure 5). Pruritus Global Score correlated with objective measurement of seconds spent itching based on camera recordings ($r = 0.81$; $P < 0.0001$). PVAS and TEWL also were correlated ($r = 0.277$; $P = 0.0071$). Hydration did not correlate with any parameters.

Discussion

In this blinded, randomized, controlled study we found that lokivetmab was able to abolish flares and pruritus when given on the very first day of allergen challenge. We found that, in the first two weeks of the study, oclacitinib, lokivetmab and prednisone had lower dermatitis scores then ciclosporin. We also found that, when all sites were considered, oclacitinib and lokivetmab

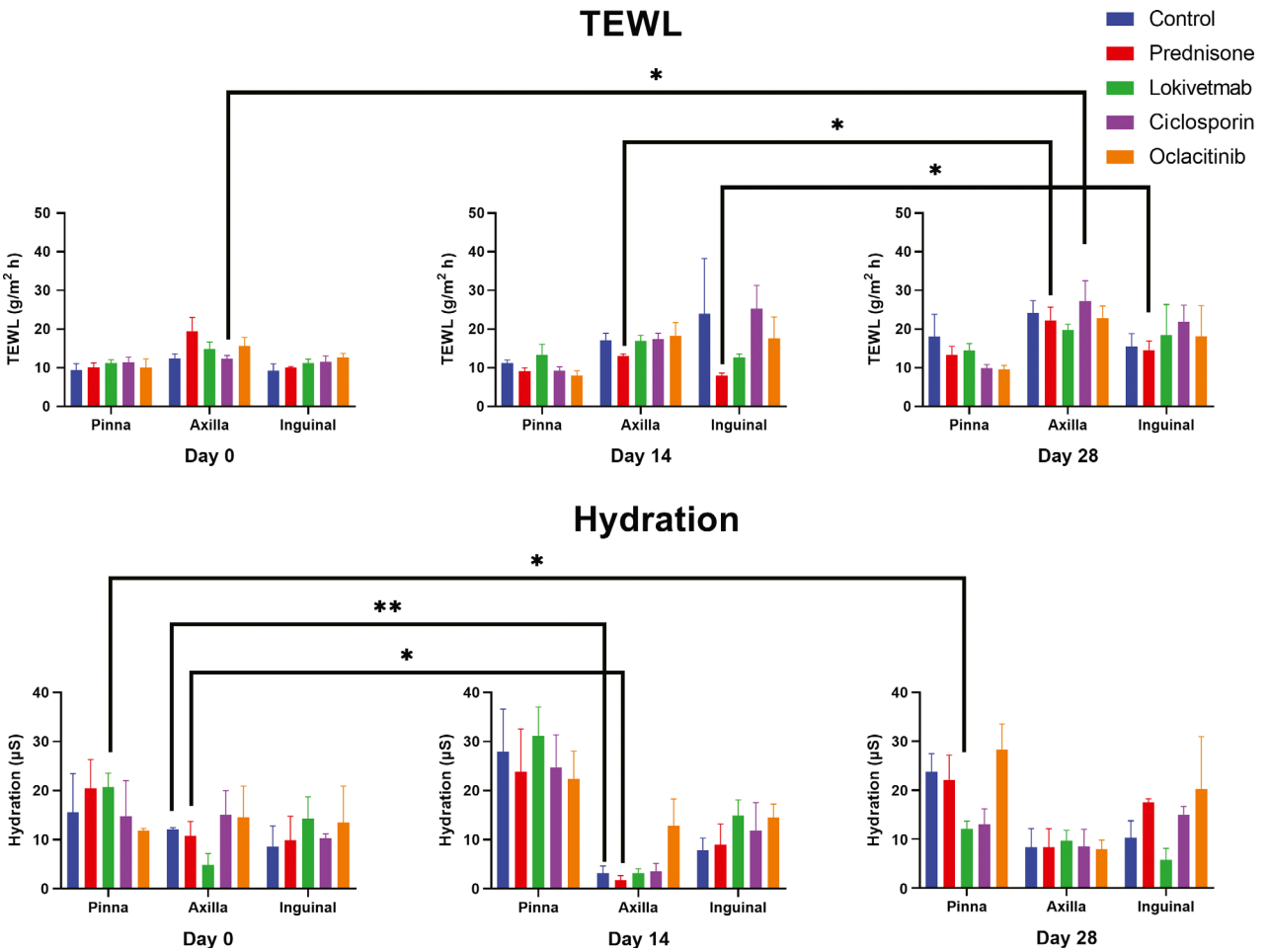

Figure 4. Composite showing transepidermal water loss (TEWL) and hydration at various time points for different body locations and all treatment groups.
In the ciclosporin group, for the axilla, significant increase of TEWL was noted at the end of the study. In the prednisone group, significant increase of TEWL was noticed in the axilla and inguinal areas from Day (D)14 to D28, when prednisone was given every other day. No significant increases for TEWL were found in the oclacitinib and lokivetmab groups at the end of the study despite the twice weekly allergen challenge. Hydration decreased in the prednisone and control group from D0 to D14. Hydration did not change in the oclacitinib group over time and decreased in the lokivetmab group (in the pinna) at the end of the study.

increased hydration compared to the controls. The effects on TEWL were varied and no definitive conclusions could be made.

Many of the findings on the clinical efficacy are consistent with other previous studies. For example, the speed of action of oclacitinib, prednisone and lokivetmab on pruritus was faster than for ciclosporin. This had been reported in separate clinical trials with privately owned animals.[1-3] It is important to note how, in our study, the effect of prednisone decreased once it was given once daily and every other day, compared to the efficacy of the induction period of twice daily administration. The efficacy of lokivetmab seen in our study was consistent with a report of the ability of lokivetmab to prevent pruritus and flares of dermatitis when used in a proactive fashion.[15] In our study, the injection was given on the day of the first allergen challenge, 1 h before allergen challenge, and thus it was consistent with a proactive protocol. Clinical flare of AD was largely prevented in the lokivetmab group, highlighting the importance of interleukin (IL)-31 in the early stages of the allergic cascade.

A few points worth addressing are the choices of scoring system. Although newer scoring systems[15,16] are available, CADESI-03 was selected for this study for the sake of consistency and comparison with other studies that had been done using this colony. In hindsight, the authors also could have used new scoring systems besides CADESI-03 to comply with more current recommendations for clinical trials. For the assessment of pruritus, we were able to do camera recordings and this provides a more objective assessment of pruritus. In the past we have documented cases in which CADESI scores and pruritus did not correlate, whereas in the present study, CADESI-03 and pruritus scores were significantly correlated. Yet, it is important not to overlook the fact that some individual dogs can be very pruritic and have minimal dermatitis, and vice versa.

This study has important limitations including the very small number of dogs in each group and the consequent impact of variability on statistical analysis. Despite the small sample size, valuable information is provided by examining treatments in a controlled setting with no confounding factors due to environment or dietary

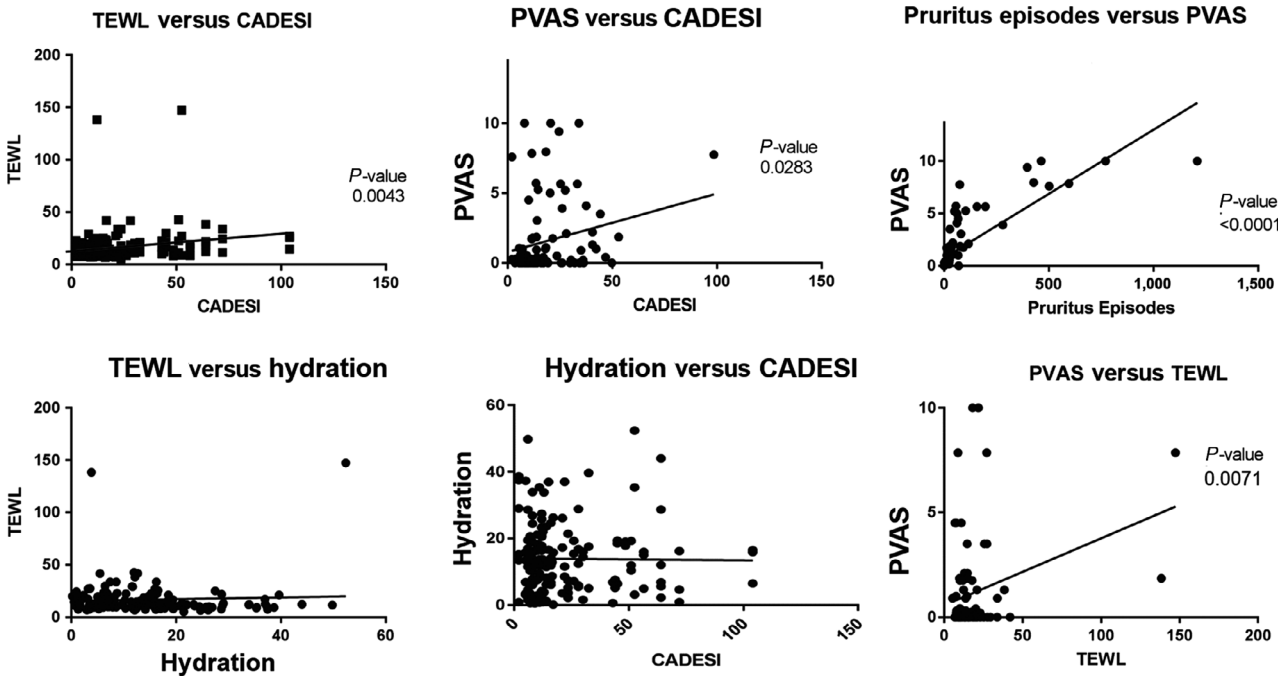

Figure 5. Composite of figures showing correlations between clinical scores of dermatitis and pruritus with transepidermal water loss (TEWL) and hydration.
Although TEWL positively correlated with CADESI and pruritus, hydration did not correlate with any clinical parameter.

differences. The number of dogs was determined by the size of the colony. A more ideal design would have been a cross-over such that each dog was exposed to all treatments, thereby serving as its own control and undergoing each treatment. Although this approach helps to decrease variability and to increase the number of dogs per treatment group, it does require wash-out periods between treatments and significantly increases the cost (due to research facility per diem rates per dog) and duration of the trial. These factors prevented the investigators from conducting this trial in a cross-over design.

Studies on skin barrier function and the effect of medications on it are challenging and difficult to interpret due to the limited ways we have to assess skin barrier function, the variability of the methodologies used and the unknown significance for some of them.[9,17] For example, measurement of TEWL is controversial due to variability and the meaning of hydration in atopic dogs is still under discussion. Bearing this in mind, a few studies have evaluated the effects of treatments and skin barrier function. In a previously published study on oclacitinib and TEWL,[18] the effects were varied and increased TEWL was found in the inguinal area in the oclacitinib-treated dogs compared to the placebo group. In the present study, although the dogs on placebo and ciclosporin challenged with allergen had increased TEWL (e.g. in the axilla), no increase was seen in the oclacitinib and lokivetmab groups despite the allergen challenges. That can be considered a positive effect. One published study evaluated TEWL during lokivetmab therapy.[19] This study was longer than ours (it lasted 12 weeks and involved three injections versus four weeks and one injection in our study) and was done on privately owned dogs. The authors reported that TEWL decreased in the majority of body sites examined. The authors calculated a mean TEWL score for each dog/day because the TEWL did not decrease in all body sites. In our study, we did not calculate the average TEWL for each dog combining all body sites and we examined fewer body sites.

When using AUC for analysis, in our study ciclosporin and prednisone also had a decreased AUC for TEWL compared to the controls, which can be consistent with decreased inflammation because severity of dermatitis (CADESI-03 scores) and TEWL positively correlated in our study. In a study published on the effects of ciclosporin on TEWL, a decrease was reported in privately owned dogs for inguinal area and antebrachial fossa;[20] whereas in our study a worsening of TEWL was seen in the axillae at the end of the study compared to the baseline. It is important to note that the study on privately owned dogs had a larger number of subjects and that likely increased the ability to detect a positive effect.

To the best of the authors' knowledge, no previous study has investigated the effects of various treatments for cAD on hydration. The positive effect on hydration observed for lokivetmab- and oclacitinib-treated dogs has unclear clinical significance because hydration did not correlate with other clinical parameters in our study and it is still unclear whether decreased hydration is a feature of atopic dogs, as it is in people.[9] Clearly, more studies are needed to investigate this topic further.

In summary, prednisone, oclacitinib and lokivetmab had positive clinical effects on dermatitis in the first two weeks of the treatment. Importantly, in our colony, prednisone did not control clinical signs well when given on alternate day regimen. A clinically relevant outcome of our study was the ability of a single injection of lokivetmab immediately before first allergen challenge to prevent development of pruritus and dermatitis despite allergen challenges. This emphasizes the relevance of IL-

31 and the benefit of blocking this cytokine early on in the inflammatory cascade triggered by allergen exposure. This approach appeared superior to other strategies, including use of broad-spectrum drugs such as oral glucocorticoids and ciclosporin. The effects of these treatments on skin barrier parameters were varied and the relevance of hydration in cAD remains unclear at this point. It is concluded that we need reliable, sensitive, noninvasive methodologies to expand our knowledge of the effects of cAD therapies on skin barrier function.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1. Graph of the area under the curve (AUC) and standard deviations (SD) for both the acute phase (Day (D)0 to D14) and chronic phase (D15 to D28) for each treatment group.
Figure S2. Means and standard deviations of Pruritus Visual Analog Scale (PVAS) values (also called Global Pruritus Assessment) for each group over time.
Figure S3. Means and standard deviations (SD) of duration (s) of pruritic acts logged in 30 min of camera recordings for each treatment group over the course of the study.
Figure S4. Area under the curve (AUC) and standard deviation for both acute and chronic phases.

Résumé
Contexte – Aucune étude n'a directement comparé les différentes options thérapeutiques de la dermatite atopique canine et leurs effets sur la barrière cutanée.
Hypothèses/Objectifs – Comparer la prednisone, l'oclacitinib, la ciclosporine et le lokivetmab dans le traitement de la dermatite atopique.
Sujets – Dix neufs chiens beagles atopiques.
Matériels et méthodes – Etude contrôlée, en aveugle. Les chiens ont été testés avec des allergènes deux fois par semaine et répartis au hasard entre oclacitinib, ciclosporine, lokivetmab, prednisone ou aucun

traitement pendant quatre semaines. Les lésions et le prurit ont été déterminés à jour 0 et après chaque provocation. La perte d'eau trans-épidermique (TEWL) et l'hydratation ont été mesurés à J0, J14 et J28 (pavillon, pli axillaire et inguinal). L'aire sous la courbe (AUC) a été calculée pour le CADESI-03 (Canine Atopic Dermatitis Extent and Severity Index, 3rd iteration), prurit, TEWL et hydratation. Pour le CADESI, l'AUC des deux premières semaines a été comparé à celle des deux dernières semaines.
Résultats – Pour le CADESI, une probabilité ANOVA- maximale limitée, a montré un effet du temps (*P = 0034*) et de l'interaction temps x groupe (*P = 0.0169*). Au cours des deux premières semaines, la prednisone et l'oclacitinib étaient significativement plus faibles que les contrôles (respectivement, *P = 0.019* et *P = 0.015*). Le lokivetmab prévenait les poussées. En raison de la variabilité, aucune différence significative pour le prurit n'a été observée parmi les groupes. La TEWL a augmenté avec le temps pour les contrôles (*P = 0.0237*) et la ciclosporine (*P = 0.04*, axillaire, D28 versus D0) mais pas dans les groupes oclacitinib et lokivetmab. Le CADESI-03 corrèle avec TEWL (*P = 0.0043*) et le prurit (*P = 0.0283*). L'hydratation ne corrèle avec aucun des paramètres. L'hydratation diminue dans les groupes contrôles et prednisone (respectivement axillaire, D14 versus D0, *P = 0.004* et *P = 0.027*). L'AUC pour l'hydratation, dans le temps, était plus élevée pour le lokivetmab et l'oclacitinib que les contrôles (respectivement *P = 0.014* et *P = 0.04*).
Conclusions et importance clinique – Le lokivetmab prévient les poussées lorsqu'administré avant provocation. L'oclacitinib et le lokivetmab ont des effets positifs sur les paramètres de barrière cutanée.

Resumen
Introducción – ningún estudio ha comparado directamente las diversas opciones de tratamiento para la dermatitis atópica canina y sus efectos sobre la barrera cutánea.
Hipótesis/Objetivos – comparar el tratamiento con prednisona, oclacitinib, ciclosporina y lokivetmab frente a la dermatitis atópica.
Animales – Diecinueve perros beagle atópicos.
Métodos y materiales – Estudio controlado, ciego. Los perros fueron expuestos a alergenos dos veces por semana y se asignaron al azar a oclacitinib, ciclosporina, lokivetmab, prednisona o ningún tratamiento durante cuatro semanas. La dermatitis y el prurito se evaluaron al inicio del estudio y después de cada desafío. La pérdida de agua transepidérmica (TEWL) y la hidratación se midieron al inicio, día (D) 14 y D28 (orejas, axila, ingle). Se calculó el área bajo la curva (AUC) para el índice de gravedad y extensión de la dermatitis atópica canina, tercera versión (CADESI-03), prurito, TEWL e hidratación. Para el CADESI, el AUC de las primeras dos semanas se comparó con el de las últimas dos semanas.
Resultados – para el CADESI, el ANOVA de máxima probabilidad restringida mostró efecto del tiempo (*P* = 0,034) y la interacción grupo x tiempo (*P* = 0,0169). En las primeras dos semanas, la prednisona y el oclacitinib fueron significativamente más bajos que los controles (*P* = 0,019 y *P* = 0,015, respectivamente). Lokivetmab previno los recidivas. Debido a la variabilidad, no se observaron diferencias significativas en el prurito entre los grupos. La TEWL aumentó con el tiempo en los controles (*P* = 0,0237) y ciclosporina (*P* = 0,04, axila, D28 comparado con D0) pero no en los grupos oclacitinib y lokivetmab. CADESI-03 estuvo correlacionado con TEWL (*P* = 0,0043) y prurito (*P* = 0,0283). La hidratación no se correlacionó con ningún parámetro. La hidratación disminuyó en los controles y en el grupo de prednisona (axila, D14 comparado con D0, *P* = 0,004 y *P* = 0,027, respectivamente). AUC para la hidratación, con el tiempo, fue mayor para lokivetmab y oclacitinib que en los controles (*P* = 0,014 y *P* = 0,04, respectivamente).
Conclusiones e importancia clínica – Lokivetmab previno la reaparición de signos clínicos cuando se administró antes del desafío. Oclacitinib y lokivetmab tienen algunos efectos positivos sobre los parámetros de barrera cutánea.

Zusammenfassung
Hintergrund – Es gibt bisher keine Studien, die die verschiedenen Behandlungsmethoden der atopischen Dermatitis des Hundes und ihre Auswirkungen auf die Hautbarriere direkt verglichen haben.
Hypothese/Ziele – Ein Vergleich der Behandlung der atopischen Dermatitis des Hundes mit Prednisolon, Oclacitinib, Ciclosporin und Lokivetmab.
Tiere – Neunzehn atopische Beagles.
Methoden und Materialien – Eine kontrollierte Blindstudie. Es wurde an den Hunden zweimal wöchentlich eine Provokation mit Allergen durchgeführt und die Hunde zufällig für eine 4 wöchige Behandlung mit Oclacitinib, Ciclosporin, Lokivetmab, Prednisolon und in eine Gruppe ohne Behandlung eingeteilt. Es wurden die Dermatitis und der Juckreiz an der Ausgangsbasis und nach jeder Provokation beurteilt. Der transepidermale Flüssigkeitsverlust (TEWL) und der Status der Hydrierung wurden am Anfang, am Tag (D) 14 und D28 (Pinnae, Achseln, Leiste) gemessen. Die Fläche unter der Kurve (AUC) wurde für den Canine Atopic Dermatitis Extent and Severity Index, dritte Ausgabe (CADESI-03), Juckreiz, TEWL und die Hydrierung kalkuliert. Für den CADESI wurde die AUC der ersten zwei Wochen mit jenen der letzten zwei Wochen verglichen.
Ergebnisse – Für CADESI zeigte ein restricted maximum-likelihood ANOVA eine Auswirkung der Zeit (*P* = 0034) und Gruppe x der Zeitinteraktion (*P* = 0,0169). In den ersten beiden Wochen waren die Gruppen mit

Prednisolon und Oclacitinib signifikant niedriger als die Kontrollen ($P = 0,019$ bzw $P = 0,015$). Lokivetmab konnte Schübe verhindern. Aufgrund der Variabilität wurden keine signifikanten Unterschiede beim Juckreiz zwischen den Gruppen beobachtet. Die TEWL nahm mit der Zeit bei den Kontrollen ($P = 0,0237$) und bei Ciclosporin ($P = 0,04$, Achsel, D28 versus D0) zu, blieb aber in den Oclacitinib und Lokivetmab Gruppen gleich. CADESI-3 korrelierte mit dem TEWL ($P = 0,004$) und dem Juckreiz ($P = 0,02383$). Die Hydrierung korrelierte mit keinem der Parameter. Die Hydrierung nahm bei den Kontrollen sowie in der Prednisolongruppe ab (Achsel, D14 versus D0, $P = 0,004$ bzw $P = 0,027$). Die AUC für die Hydrierung wurde mit zunehmender Zeit größer, wobei sie bei den Lokivetmab und Oclacitinib Gruppen höher war als bei den Kontrollgruppen ($P = 0,014$ bzw $P = 0,04$).
Schlussfolgerungen und klinische Bedeutung – Lokivetmab konnte Schübe verhindern, wenn es vor der Provokation verabreicht wurde. Oclacitinib und Lokivetmab haben einige positive Auswirkungen auf die Parameter der Hautbarriere.

要約
背景 – 犬アトピー性皮膚炎のさまざまな治療選択肢および皮膚バリアに対する効果を直接比較した研究はない。
仮説/目的 – 本研究の目的は、犬アトピー性皮膚炎に対するプレドニゾン、オクラシチニブ、シクロスポリンおよびロキベトマブ治療を比較することであった。
供試動物 – アトピーに罹患した19頭のビーグル犬。
材料と方法 – 対照群を設けた盲検試験を実施した。犬にアレルゲンを週に2回負荷し、それぞれオクラシチニブ、シクロスポリン、ロキベトマブ、プレドニゾンによる4週間の治療を施した群または無治療群に無作為に割り当てた。皮膚炎および掻痒を、開始時および各負荷後に評価した。経皮水分蒸散量(TEWL)および水和度を、開始時、14日および28日で測定した(耳介、腋窩、鼠径部)。曲線下面積(AUC)を、犬アトピー性皮膚炎の程度と重症度指数(CADESI-03)、掻痒、TEWLおよび水和度について計算した。 CADESIについては、最初の2週間のAUCを最後の2週間のAUCと比較した。
結果– – 制限付き最尤ANOVAはCADESIにおいて時間の影響(P = 0034)と群x時間の相互作用(P = 0.0169)を示した。CADESIにおいて最初の2週間で、プレドニゾンおよびオクラシチニブ群は対照群よりも有意に低かった(それぞれP = 0.019、P = 0.015)。ロキベトマブは紅斑を防いだ。ばらつきにより群間の掻痒に有意差は観察されなかった。 TEWLは、対照群(P = 0.0237)およびシクロスポリン治療群(P = 0.04、腋窩、28日目対D00日目)で時間とともに増加したが、オクラシチニブおよびロキベトマブ群では増加しなかった。 CADESI-03は、TEWL(P = 0.0043)および掻痒(P = 0.0283)と相関した。水和度はどのパラメーターとも相関しなかった。水和度は、対照群およびプレドニゾン群で減少した(腋窩、14日目対0日目、それぞれP = 0.004およびP = 0.027)。ロキベトマブおよびオクラシチニブ群の水和度のAUCは、対照群と比較して経時的に高かった(それぞれP = 0.014とP = 0.04)。
結論と臨床的重要性 – ロキベトマブは、アレルゲン負荷前に投与された際に紅斑を予防した。オクラシチニブおよびロキベトマブは、皮膚バリアパラメータにいくつかのプラスの効果を有する。

摘要
背景 — 尚无研究直接比较异位性皮炎的各种治疗方案的效果,及其对皮肤屏障的影响。
假设/目的 — 比较泼尼松、奥拉替尼、环孢素和洛基维特单抗治疗异位性皮炎。
动物 — 19只异位性比格犬。
方法和材料 — 对照、设盲研究。犬每周两次用过敏原激发,并随机分配至奥拉替尼、环孢素、洛基维特单抗、泼尼松组或不治疗组,持续4周。在基线和每次激发后评估皮炎和瘙痒。第14天(D)和28D(耳廓、腋窝、腹股沟)测量经表皮失水 (TEWL) 和水合作用基础值。计算犬异位性皮炎程度和严重指数第3版 (CADESI-03)、瘙痒、TEWL和水合能力的曲线下面积 (AUC)。对于CADESI,将前两周的AUC与后两周的AUC进行比较。
结果 — 对于CADESI,限制性最大似然法ANOVA显示时间效应(P=0034),以及组x时间互作(P=0.0169)。在前两周,泼尼松和奥拉替尼显著低于对照组(分别为P=0.019和P=0.015)。洛基维特单抗可预防复发。由于不确定性性,各组间未观察到瘙痒的显著差异。对照组(P=0.0237)和环孢素组(P=0.04,腋窝,28D vs. 0D)的 TEWL 随时间增加,但奥拉替尼组和洛基维特单抗组的TEWL未随时间增加。CADESI-03与TEWL(P=0.0043)和瘙痒(P=0.0283)相关。水合能力与任何参数均不相关。对照组和泼尼松组水合能力下降(腋窝,D14与D0,分别为P=0.004和P=0.027)。随着时间的推移,洛基维特单抗和奥拉替尼的水合能力AUC高于对照组(分别为P=0.014和P= 0.04)。
结论和临床重要性 — 过敏原激发前给予洛基维特单抗可预防复发。奥拉替尼和洛基维特单抗对皮肤屏障参数有一定积极影响。

Resumo
Contexto – Nenhum estudo comparou diretamente as várias opções de tratamento para dermatite atópica canina e seus efeitos na barreira cutânea.
Hipótese / Objetivos – Comparar o tratamento da dermatite atópica com prednisona, oclacitinib, ciclosporina e lokivetmab.
Animais – Dezenove cães atópicos da raça beagle.

Métodos e materiais – Estudo cego controlado. Os cães foram desafiados com alérgeno duas vezes por semana e randomizados para administração de oclacitinib, ciclosporina, lokivetmab, prednisona ou nenhum tratamento por quatro semanas. Dermatite e prurido foram avaliados no início e após cada desafio. A perda de água transepidérmica (TEWL) e a hidratação foram medidas no início do dia (D) 14 e D28 (pinnae, axila, virilha). A área sob a curva (AUC) foi calculada para Índice de Extensão e Gravidade da Dermatite Atópica Canina, 3ª iteração (CADESI-03), prurido, TEWL e hidratação. Para CADESI, a AUC das duas primeiras semanas foi comparada com a das duas últimas semanas.

Resultados – No CADESI, a ANOVA de máxima verossimilhança restrita mostrou efeito do tempo (P = 0034) e interação grupo x tempo (P = 0,0169). Nas duas primeiras semanas, a prednisona e o oclacitinib foram significativamente menores que os controles (P = 0,019 e P = 0,015, respectivamente). Lokivetmab evitou erupções. Devido à variabilidade, não foram observadas diferenças significativas no prurido entre os grupos. O TEWL aumentou com o tempo nos controles (P = 0,0237) e ciclosporina (P = 0,04, axila, D28 versus D0), mas não nos grupos oclacitinib e lokivetmab. CADESI-03 correlacionou-se com TEWL (P = 0,0043) e prurido (P = 0,0283). A hidratação não se correlacionou com nenhum parâmetro. A hidratação diminuiu nos grupos controle e prednisona (axila, D14 versus D0, P = 0,004 e P = 0,027, respectivamente).A AUC para hidratação, ao longo do tempo, foi maior para lokivetmab e oclacitinibe que os controles (P = 0,014 e P = 0,04, respectivamente).

Conclusões e importância clínica – O Lokivetmab preveniu os surtos quando administrado antes do desafio. Oclacitinib e lokivetmab têm alguns efeitos positivos nos parâmetros da barreira cutânea.