

Validation of the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-4, a simplified severity scale for assessing skin lesions of atopic dermatitis in dogs

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Background – Severity scales are used to grade skin lesions in clinical trials for treatment of dogs with atopic dermatitis (AD). At this time, only two scales have been validated, namely the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-3 and the Canine Atopic Dermatitis Lesion Index (CADLI). However, the high number of assessed sites makes the CADESI-3 impractical.

Hypothesis/Objectives – The aim of this study was to develop and validate a fourth version of the CADESI that is simpler and quicker to administer.

Methods – Body sites, lesions and severity grades were revised by members of the International Committee on Allergic Diseases of Animals (ICADA). The newly designed CADESI-4 was tested for its validity (i.e. content, construct and criterion), reliability (i.e. inter- and intra-observer reliability and internal consistency), responsiveness (i.e. sensitivity to change) and time to administer. Disease severity benchmarks were chosen using receiver operating characteristic methodology.

Results – The CADESI-4 was simplified in comparison to its previous version to comprise 20 body sites typically affected in atopic dogs. Three lesions (erythema, lichenification and alopecia/excoriation) were scored from 0 to 3 at each site. The CADESI-4 had satisfactory validity, reliability and sensitivity to change. On average, the time to administer a CADESI-4 was one-third that of a CADESI-3. Proposed benchmarks for mild, moderate and severe AD skin lesions are 10, 35 and 60, respectively.

Conclusions and clinical importance – The CADESI-4 is simpler to use and quicker to administer than its previous version. The ICADA recommends the CADESI-4 instead of the CADESI-3 to score skin lesions of AD in dogs enrolled in clinical trials.

Introduction

Clinical signs of canine atopic dermatitis (AD) include pruritus and skin lesions that are primary (e.g. erythema), secondary (e.g. hyperpigmentation and lichenification) or the consequence of self-trauma to relieve pruritus (e.g. excoriations and self-induced alopecia).¹ Erythema and pruritus normally coexist in the same patient but their severity is not always correlated.² As a result, clinical trial outcome measures should reflect the efficacy of tested

interventions on both atopic skin lesions and pruritus as separate parameters. Validated measuring tools are therefore needed to assess these clinical signs reliably in dogs with AD.

In 1997, the first version of the Canine Atopic Dermatitis Extent and Severity Index (CADESI) was proposed in an open trial evaluating misoprostol for treatment of canine AD.³ This scale was generated by evaluating erythema, excoriations and lichenification at 23 different body areas on a scale of none (score 0), mild (score 1), moderate (score 2) and severe (score 3).³ In 2002, the second version of the CADESI increased the number of body areas examined to 40 but kept the same lesions and severity grades.^{4,5} In an effort to generate a disease scale that was tested for validity, reliability and responsiveness,

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as recommended for severity scales used for human AD,⁶ an *ad hoc* committee of the then International Task Force on Canine AD [now International Committee on Allergic Diseases of Animals (ICADA)] proposed a third version of the CADESI in 2007.⁷ This revision increased the number of body regions to 62, added self-induced alopecia as a fourth lesion to provide a better reflection for pruritus and broadened the severity scale from four to six grades, as follows: none (score 0), mild (score 1), moderate (score 2–3) and severe (score 4–5). This CADESI-3 had acceptable content, construct, criterion, inter- and intra-observer reliability and sensitivity to change.⁷ Subsequently, the CADESI-3 cut-off values for dogs with disease in remission and those with mild, moderate and severe AD were determined using receiver operating characteristic methodology.⁸ As the CADESI-3 was, at that time, the only validated disease scale to score skin lesions of canine AD, it was recommended for use in clinical trials of atopic dogs.⁸

After 5 years of use, it became clear that the number of sites and lesions assessed in the CADESI-3 made it cumbersome and time consuming to administer. Furthermore, the complexity of the CADESI-3 led to the flourishing of 'modified CADESI scales', in which investigators either decreased the number of sites and/or changed the severity grades or the lesions assessed. These revised scales, which often misused the CADESI name, misled readers in their assumptions that the modified scales were validated, when in fact, they were not. Additionally, these modifications precluded the comparison of disease severity groups between studies. In order to alleviate the caveats of the CADESI-3, Plant and colleagues designed the Canine Atopic Dermatitis Lesion Index (CADLI), which was then validated as a severity scale for the evaluation of lesions of canine AD.⁹ A strong advantage of the CADLI is that the time required to administer it is markedly less than that of the CADESI-3.⁹

The CADESI-3 scale therefore needs to be revised in order to improve its practicality and reduce the time required to administer it, especially when scoring dogs with extensive skin lesions at the start of clinical trials.

The objectives of the present study were as follows: (i) to design a shorter version of the CADESI-3 (CADESI-4); (ii) to test its validity, reliability, sensitivity to change and the time required to administer it; and (iii) to determine cut-off benchmarks for dogs with AD of varying severity.

Materials and methods

Design of the CADESI-4

The CADESI-4 was designed to score skin lesions at specific body sites using a categorical severity scale.

Lesion type selection

In November 2011, after preliminary discussion and trial evaluation, ICADA members voted on four specific propositions. The choices were as follows: (i) to use lesions identical to those of the CADESI-3 (i.e. erythema, lichenification, excoriations and alopecia);⁷ (ii) to combine the last two lesions of the CADESI-3 (i.e. erythema, lichenification and excoriation/alopecia); (iii) to use lesion combinations similar to those of the CADLI (i.e. erythema/excoriations/erosions and alopecia/lichenification/hyperpigmentation);⁹ or

(iv) to separate the last combination and omit hyperpigmentation, which could be poorly responsive in short-term trials. The choice was made after a simple majority vote using an anonymous online survey.

Body site selection

In 2010, Favrot and colleagues studied more than 1000 dogs with AD and other pruritic dermatoses to generate criteria for the diagnosis of AD.¹⁰ The discriminating ability of multiple epidemiological, historical, clinical and IgE hypersensitivity parameters were evaluated. Ultimately, two sets of criteria with acceptable sensitivity and specificity for the diagnosis of canine AD were proposed.¹⁰ Data provided by the study's principal investigator were used to select body areas that fulfilled the following criteria for separating dogs with AD from those with other pruritic diseases: (i) a significant positive association with the diagnosis of AD (i.e. significantly more common in dogs with AD); and (ii) a high combination of sensitivity and specificity for the diagnosis of AD (i.e. sensitivity $\times$ specificity > 0.25). This ensured that body areas selected for the CADESI-4 would be commonly affected in dogs with AD compared with other pruritic diseases. Members of the ICADA voted on the body area slate using an anonymous online survey.

Severity scale selection

In November 2011, ICADA members voted using an anonymous online survey between the six-point severity scale used in the CADESI-3 and the CADLI (i.e. scores of 0–5) or the four-point scale employed in the CADESI-1 and CADESI-2 (i.e. scores of 0–3). The decision was based on earlier discussions, as well as on results of a preliminary study that tested the consistency of erythema grading among dermatology specialists using a photographic atlas (P. B. Hill, unpublished data).

Validation of the CADESI-4

The newly designed CADESI-4 severity scale was evaluated for validity, reliability, responsiveness (i.e. sensitivity to change) and the time required to administer it, as proposed by Charman and Williams.⁶

Study subjects

Clinician members of the ICADA selected dogs with AD with active lesions of any severity. The diagnosis was based on the criteria of Favrot *et al.*,¹⁰ after ruling out other pruritic dermatoses and verifying an absence of actively infected skin lesions that could influence the grading of the AD lesions. As food ingredients have now been accepted as flare factors of AD in some dogs hypersensitive to such allergens,^{11,12} a food restriction–provocation trial was not required prior to case selection. Dogs could be selected whether or not they were currently being treated for AD. To ensure a wide range of lesion scores, atopic dogs in clinical remission and those considered by both the owner and the investigative clinician to have severe AD were specifically recruited. Finally, normal dogs were selected if they had no history of or lesions consistent with AD or other dermatological diseases at the time of evaluation.

Evaluation of validity

Evaluating the validity of a scale means determining whether it measures what it is intended to measure effectively; this consists of an assessment of its content, construct and criterion.⁶

Evaluation of content. The content of a scale reflects its ability to assess all the relevant content, or domains, based on the judgement of one or more experts.⁶ The validation of the CADESI-4 content was made by approval of a set of skin lesions, body sites and a severity grading scheme by a simple majority vote of ICADA members in an anonymous online survey.

Evaluation of construct. The construct of a scale represents its capacity to agree with other related variables and measures of

the same construct, with which, at least in theory, it ought to agree.⁶

As CADESI-4 scores should theoretically correlate with those obtained with previously validated severity scales for canine AD skin lesions, i.e. the CADESI-3^{7,9} and the CADLI,⁹ the construct of this new scale was evaluated by having the same clinician successively grade the CADESI-3, CADESI-4 and CADLI on the same patient with active AD within minutes of each other. Correlations between CADESI-4 and CADESI-3 as well as between CADESI-4 and CADLI were then assessed using Spearman's rank correlation coefficients. The Prism 5.0 software (Graphpad, San Diego, CA, USA) was used for this and all other statistical calculations, unless otherwise specified. The significance was set at $P < 0.05$.

Evaluation of criterion. The criterion of a scale denotes its aptitude to correlate with other measures of the disease.⁶

At first, it would seem logical to evaluate the correlation between CADESI-4 values and pruritus scores, because skin lesions and itch usually coexist in dogs with AD. However, results from a recent study have suggested that, in dogs with AD, erythema can be present while pruritus is in the normal range, or vice versa.² As a result, evaluating the correlation between pruritus scores and CADESI-4 values does not appear sensible to evaluate the criterion of this new scale.

In the absence of a 'gold standard' to measure the severity of AD in dogs, we chose to determine the correlation between CADESI-4 values and subjective global assessments of skin lesion severity, as done recently for the Patient-Oriented Eczema Measure (POEM) scale in humans with AD.¹³ To evaluate the criterion of the CADESI-4, the same clinician scored it in dogs with AD at two visits, 1 month apart. At each time point, one of the dog's owners was asked to assess the severity of skin lesions subjectively while not taking into account that of pruritus. The Owner Global Assessment of Severity (OGA-S) was subjectively rated as follows: score 1, no skin lesions (i.e. AD in remission); score 2, mild AD; score 3, moderate AD; and score 4, severe AD. Likewise, at each time point, another clinician, different from the ones grading the initial CADESI-4, subjectively assessed the severity of skin lesions using the same scale as above [i.e. the Investigator Global Assessment of Severity (IGA-S)]. We determined the correlation between CADESI-4 and OGA-S or IGA-S using Spearman's rank correlation coefficients.

Evaluation of reliability

The reliability of a scale assesses whether it measures what it is intended to measure effectively and in a reproducible fashion; its evaluation typically consists of an assessment of the inter- and intra-observer reliabilities as well as internal consistency.⁶

Evaluation of interobserver reliability. In order to assess this parameter, measurements made by two or more observers must be compared to determine if they produce similar results.⁶

Firstly, the CADESI-4 was independently scored in dogs with active AD by two different clinicians working at the same institution, within 1 h of one another. The correlation between the scores from the two investigators was calculated using Spearman's rank correlation coefficient. Furthermore, the sets of score pairs were compared using Wilcoxon's signed rank test.

In a second assessment of the CADESI-4 interobserver reliability, but this time with multiple evaluators, six veterinarians attending a dermatology training course [European School of Advanced Veterinary Studies (ESAVS), Vienna, 2012] graded the skin lesions of five dogs with AD of varying severity within a 1 h time frame. Only two of these veterinarians had used the CADESI-4 before. The other four had been sent a copy of CADESI-4 and CADLI prior to the meeting, but had not trained together to use these scales. Three of the six investigators had worked at the same institution. The correlation between all possible CADESI-4 paired values (i.e. between all available pairs of clinicians) was done using Spearman's rank correlation

coefficient; the sets of score pairs were also compared using Wilcoxon's signed rank test.

Evaluation of intra-observer reliability. This factor is normally assessed by determining whether two measurements made by the same observer, on two or more distinct occasions, yield similar results.⁶

In order to evaluate this parameter, the same clinician scored the CADESI-4 in dogs with active AD twice on the same visit, but at least 3 h apart. The correlation between the scores was determined using Spearman's rank correlation coefficient, and value pairs were also compared using Wilcoxon's signed rank test.

Evaluation of the internal consistency

The assessment of internal consistency involves establishing whether the scores from the different components of the scale correlate with each other and with the total score. In other words, it assesses whether or not the various items composing the scale measure the same attribute.⁶

In order to determine the internal consistency, we used all the CADESI-4 assessments in any dog with active AD, although no more than one evaluation per dog per visit was included (for the first visit, only the first CADESI-4 graded by the first clinician was used). Total scores for erythema, lichenification and excoriations/alopecia were calculated by adding all severity values obtained at all sites for each lesion. Spearman's rank correlation coefficients were calculated between pairs of each of the three individual total lesion scores, as well as between each lesion total score and the CADESI-4 values for the same dog. Additionally, Cronbach's α was calculated, as done previously for the CADLI,⁹ using free online software (<http://www.wessa.net>; last accessed 1 October 2013). Finally, the percentages of the final CADESI-4 scores represented by the total scores for each lesion were determined.

Evaluation of sensitivity to change

The sensitivity to change reflects the ability of a scale to detect clinically meaningful changes in disease severity in response to healthcare interventions.⁶

We tested this parameter for the CADESI-4 as done for the CADESI-3.⁷ Dogs with active AD were treated with anti-allergic interventions of any type or combination by their dermatologist for a minimum of 1 month. At the re-evaluation visit, the dogs' owners were asked to grade the treatment efficacy subjectively using a five-point categorical scale [the Owner Global Assessment of Efficacy (OGA-E)], as follows: score 0, no efficacy; score 1, poor efficacy; score 2, fair efficacy; score 3, good efficacy; and score 4, excellent efficacy. The clinician who saw the dog initially also graded his/her perception of treatment efficacy using an identical five-point scale to yield an Investigator Global Assessment of Efficacy (IGA-E) score. The clinician subsequently scored the CADESI-4 to obtain a post-treatment value. The percentage change from pretreatment (i.e. baseline) was then calculated and transformed into a five-point categorical improvement scale as follows: score 0, increase in CADESI-4; score 1, <25% reduction in CADESI-4 during treatment; score 2, 25–49% reduction in CADESI-4; score 3, 50–74% reduction in CADESI-4; and score 4, ≥75% reduction in CADESI-4. Finally, we correlated the CADESI-4 improvement scale and the IGA-E or OGA-E using Spearman rank correlation coefficients.

Evaluation of scoring time

The time taken to score the CADESI-4, CADESI-3 and CADLI by experienced clinician members of the ICADA was recorded to the nearest minute. The scoring times were compared using nonparametric repeated-measures ANOVA (Friedman test) followed by Dunn's multiple comparison *post hoc* tests.

In order to test whether previous experience of using the CADESI-4 influenced the time to administer it, the scoring times for two clinicians at the first visit were compared (see 'Evaluation of interobserver reliability' section above for methodology). Clinicians were

grouped into those who were ICADA members (i.e. 'experienced' CADESI-4 users) and those who were not (the latter were most often visitors, residents or interns, i.e. CADESI-4 'novices'). The times to score the CADESI-4 were compared between groups of clinicians using Wilcoxon's signed rank test.

Finally, in order to assess whether AD of increasing severity, as estimated by rising CADESI-4 values, had an influence on the scoring time, the CADESI-4 values and scoring time were correlated using Spearman rank correlation coefficients. For this analysis, only the first CADESI-4 scored at each visit was used.

Determination of CADESI-4 disease severity cut-off values

We used the same method to calculate CADESI-4 cut-off benchmarks for increasing severities of AD as for the CADESI-3.⁸ For each CADESI-4 assessment, another investigator and the dog's owner were instructed to assess the severity of AD subjectively (i.e. IGA-S and OGA-S) as described above for the validation of the CADESI-4 criterion. Normal dogs and those assessed by owners and clinicians to have AD in remission or severe AD were also included.

Initially, IGA-S and OGA-S were compared using Spearman rank correlation coefficients. If they were correlated, cut-off values for mild, moderate and severe AD and for AD in remission/normal dogs were calculated with receiver operating characteristic methodology using only the IGA-S, as described previously.⁸ If the IGA-S and OGA-S were not correlated, the benchmarks were also determined with the OGA-S, and cut-off values would be reconciled between those obtained using the investigator- and owner-assessed severity scores.

Results

Design of the CADESI-4

Lesion type selection

The majority of ICADA respondents voted for a set of three lesions derived from those scored in the CADESI-3. We selected erythema (as a marker of acute inflammation), lichenification (as a marker of chronic disease) and the combination of excoriation and alopecia as markers of pruritus. The 'self-induced' qualifier used for alopecia in the CADESI-3 was dropped because of the occasional difficulty of correctly assessing whether hair loss is necessarily secondary to pruritic behaviour.

Body site selection

Examination of study data¹⁰ led to the selection of the following 11 body sites that met the preset criteria. These sites are ranked as follows by decreasing sensitivity $\times$ specificity (data not shown):¹⁰ (i) hindfeet; (ii) ear pinnae; (iii) forefeet; (iv) axillae; (v) lips; (vi) flexural areas; (vii) genitalia or ventral tail; (viii) lateral thorax or flanks; (ix) elbows; (x) hindlimbs; and (xi) abdomen and/or inguinal areas.

These body sites were then compared with those scored in the CADESI-3, and they were further refined by taking into account the practicality and relevance of combinations. For example, while combining all the CADESI-3 pedal sites was considered feasible and logical, scoring all flexural body areas as one single site was deemed impractical. For pinnae, only the concave side was chosen because it is more commonly affected than the convex aspect in dogs with AD.¹ In all, 20 sites were selected (Figure 1). This combination

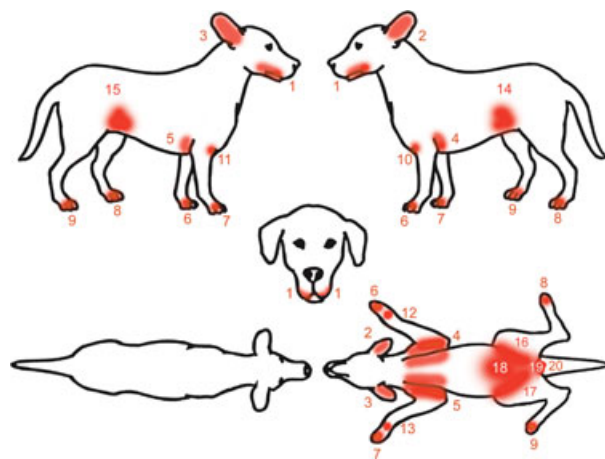


Figure 1. Body sites evaluated in the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-4.

of lesions was agreed upon by >75% of ICADA respondents.

Severity scale selection

More than 67% of the ICADA members voted to select the four-point severity scale consisting of none (score 0), mild (score 1), moderate (score 2) and severe (score 3). Furthermore, results from the dermatology specialist survey on the consistency of erythema grading suggested that this four-point scale demonstrated significantly higher agreement compared with the six-point severity scale used in the CADESI-3 (P. B. Hill, unpublished observations).

Establishment of the CADESI-4

The CADESI-4 was designed to comprise 20 body sites, less than a third of the number of sites assessed in the CADESI-3 (Figure 1). There were three lesions and four severity grades, giving a maximal score of $20 \times 3 \times 3 = 180$ (compared with 1240 in the CADESI-3). A sample of the CADESI-4 grading sheet in Microsoft Word, Excel and an atlas for training purposes can be found in Tables S1 and S2 and Figure S1, respectively, in Supplementary material.

Validation of the CADESI-4

Study subjects

In all, 39 dogs with active AD (including eight dogs with severe AD), 31 dogs with AD in remission and 30 normal dogs were selected. Dog breeds, ages and sexes were considered representative of the population of dogs relevant to each subject category (data not shown).

Evaluation of validity: content

The body sites were selected because of their high prevalence in atopic dogs and a high sensitivity and specificity for the diagnosis of AD;¹⁰ they were accepted by a majority of ICADA members.

Evaluation of validity: construct

The CADESI-3, CADESI-4 and CADLI were scored successively by the same clinician in 31 dogs with active AD

of varying severity. The CADESI-4 values were significantly correlated with those of the two other scales (Spearman $r = 0.86$ for both; $P < 0.0001$; Figure 2).

Evaluation of validity: criterion

The CADESI-4 was assessed at two different visits for 30 dogs and at one visit for one dog, thereby providing 61 pairs of CADESI-4 and global assessments of severity by owners or investigators. The CADESI-4 values were significantly correlated with OGA-S and IGA-S grades (Spearman $r = 0.64$ and 0.72 , respectively; $P < 0.0001$ for both).

Evaluation of reliability: interobserver

The CADESI-4 scores generated by two different clinicians within an hour of each other on 31 dogs with AD

were significantly correlated (Spearman $r = 0.82$; $P < 0.0001$; Figure 3, left panel). Both scores by the same investigator were not significantly different (Wilcoxon's signed rank test, $P = 0.49$).

Likewise, the evaluation of this parameter with multiple raters, most of whom had never used the scale beforehand, showed that CADESI-4 values were significantly correlated between investigator pairs (Spearman $r = 0.48$; $P = 0.0001$); these value pairs were not significantly different (Wilcoxon's signed rank test, $P = 0.63$).

Evaluation of reliability: intra-observer

Two CADESI-4 evaluations by the same clinician at least 3 h apart on 31 dogs with AD were significantly correlated (Spearman $r = 0.97$; $P < 0.0001$; Figure 3, right

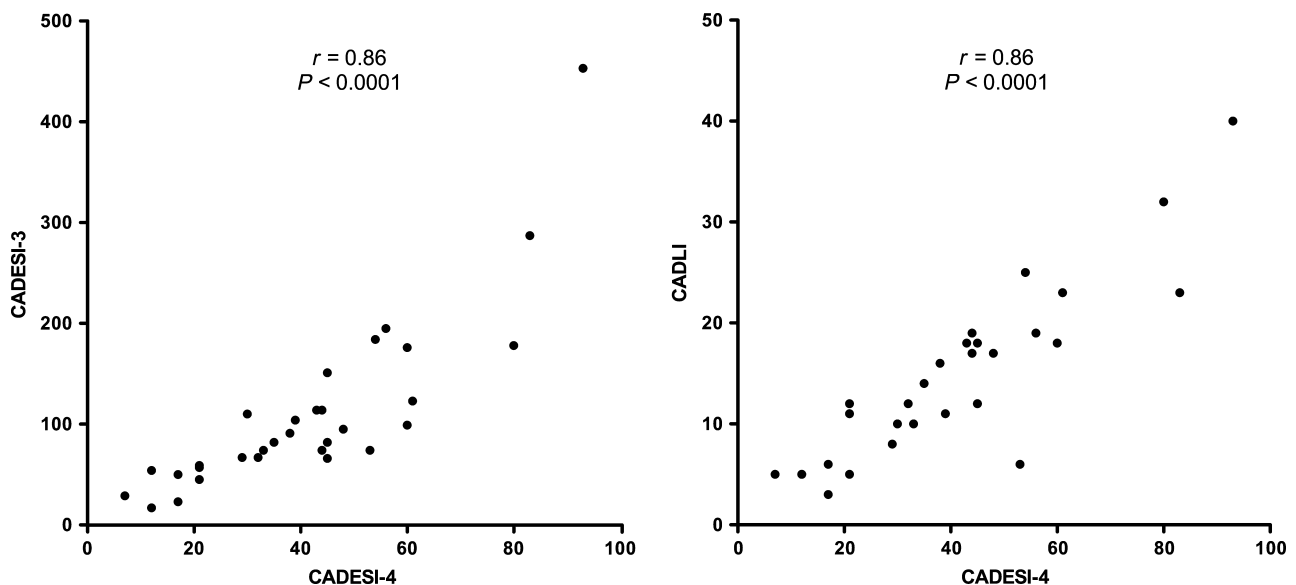


Figure 2. Construct evaluation for CADESI-4, showing correlation of the CADESI-4 with the CADESI-3 (left panel) and Canine Atopic Dermatitis Lesion Index (CADLI; right panel).

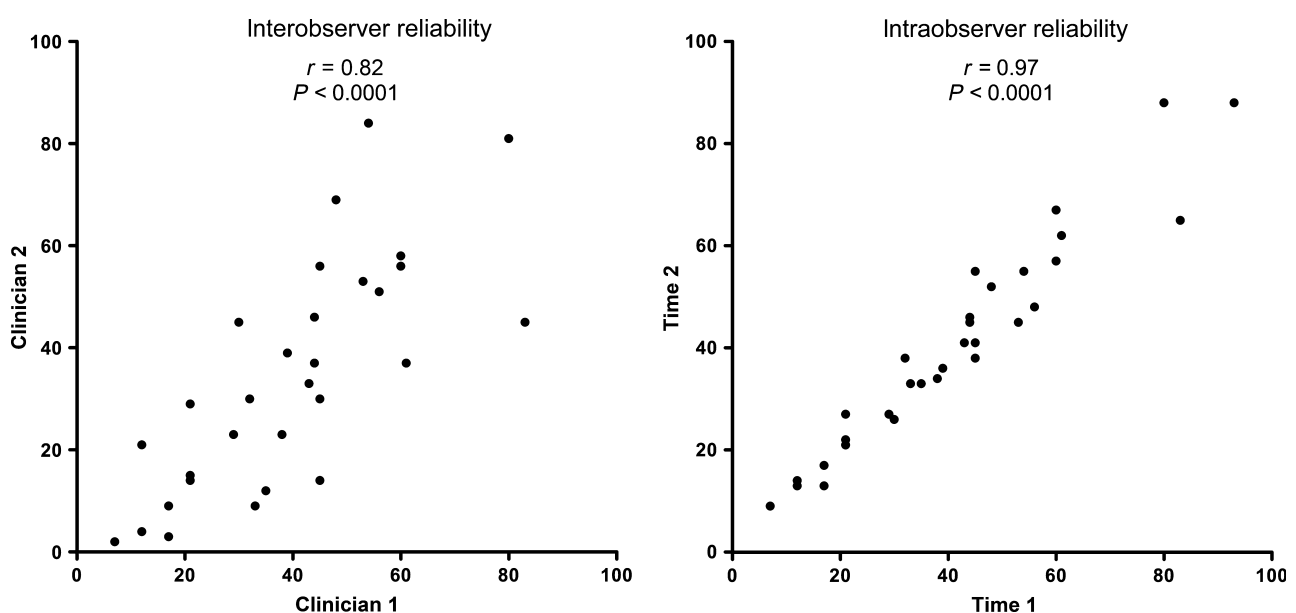


Figure 3. Reliability evaluation for CADESI-4, showing inter- (left panel) and intra-observer reliability (right panel).

panel). The paired values were not significantly different (Wilcoxon's signed rank test, $P = 0.10$).

Evaluation of reliability: internal consistency

The CADESI-4 evaluations of 31 dogs with active AD, 30 of which were also re-evaluated at a second visit at least 1 month later, yielded 61 comparisons. The total scores for each individual lesion were significantly correlated with each other as well as with the total CADESI-4 values (Table 1). Cronbach's α , a coefficient of internal consistency, was 0.84 when all lesions were included. This value is consistent with good internal consistency.

The erythema scores represented approximately half (median, 54%; range, 0–100%) of the total CADESI-4, while the lichenification and excoriation/alopecia scores represented one-quarter (median, 24%; range, 0–50%) and one-fifth of the total score (median, 21%; range, 0–90%), respectively.

Evaluation of reliability: sensitivity to change

The CADESI-4 scores from 30 atopic dogs before and 1 month after treatment were analysed. The percentage change from the pretreatment CADESI-4 score was significantly correlated with both owner (OGA-E) and investi-

gator (IGA-E) global assessments of efficacy (OGA-E, Spearman's $r = 0.65$; IGA-E, $r = 0.79$; both $P < 0.0001$).

Evaluation of scoring time

The CADESI-3, CADESI-4 and CADLI were used to score skin lesions in 31 dogs with active AD. The scoring times were significantly different (Friedman repeated-measures ANOVA, $P < 0.0001$; Figure 4, left panel). The CADLI took less time to score (median, 1 min) than the CADESI-4 (median, 4 min) and the CADESI-3 (median, 12 min). The time to score the CADESI-4 was significantly shorter for 'experienced' than 'novice' users (Wilcoxon's signed rank test, $P < 0.0001$). The latter group also had greater variability (standard deviation for experienced users, 1.4; novice users, 5.3; Figure 4, right panel). The CADESI-4 values were not significantly correlated with scoring times (Spearman's $r = 0.007$; $P = 0.96$), indicating that it did not generally take longer to assess dogs with high scores.

Determination of CADESI-4 disease severity cut-off values

As both investigator- (IGA-S) and owner-assessed values (OGA-S) were significantly correlated (Spearman's $r = 0.73$; $P < 0.0001$), the receiver operating characteristic calculations were based only on IGA-S scores. The CADESI-4 values from 30 normal dogs, 31 with AD in remission, and 36 with mild, 24 with moderate and 14 with severe disease were used to determine the severity cut-off values. We established the following CADESI-4 intervals to separate disease severity categories: normal dogs, <10 ; AD in remission, <10 ; mild AD, 10–34; moderate AD, 35–59; severe AD, ≥ 60 . In other words, benchmarks for mild, moderate and severe AD were 10, 35 and 60, respectively.

Table 1. Canine Atopic Dermatitis Extent and Severity Index (CADESI)-4 internal consistency correlation coefficients

	Erythema	Lichenification	Excoriations/ alopecia
Erythema			
Lichenification	0.62 **		
Excoriations/alopecia	0.35 *	0.47 **	
CADESI-4	0.85 **	0.82 **	0.69 **

* $P < 0.01$, ** $P < 0.001$.

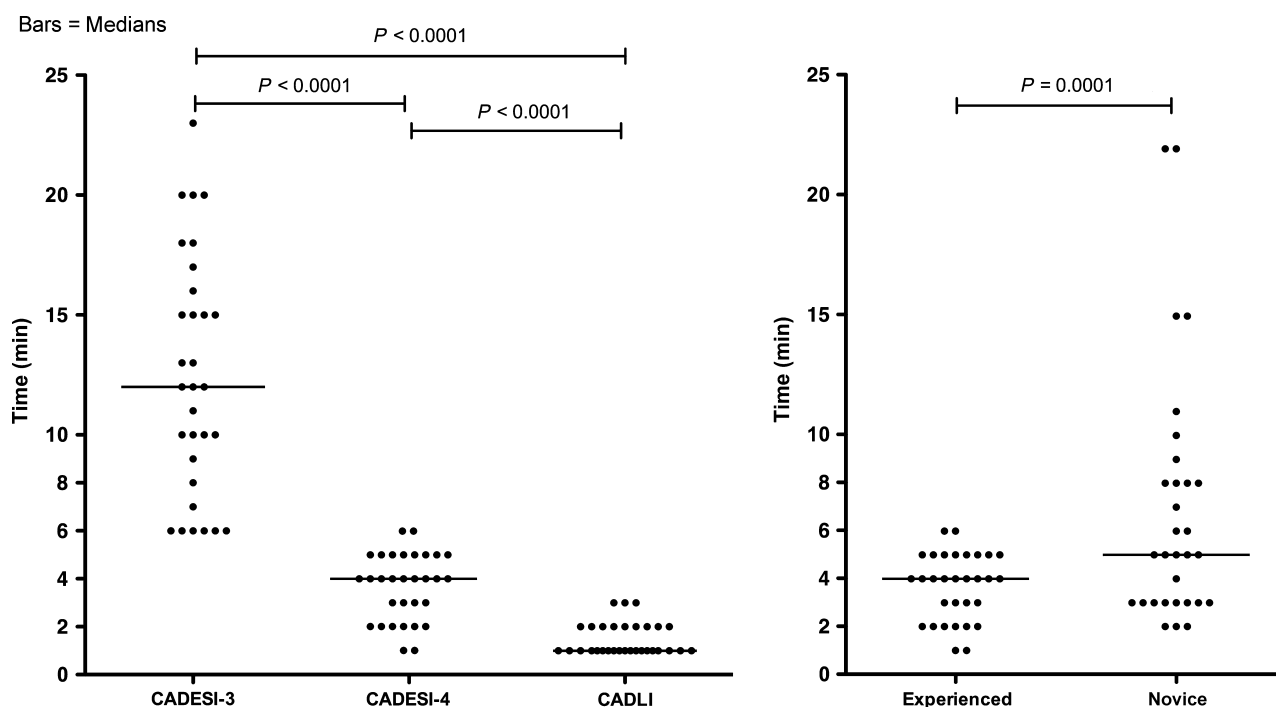


Figure 4. Time to administer the scoring system. Left panel shows a comparison of scoring times for the CADESI-3, CADESI-4 and CADLI; right panel shows a comparison of scoring times between 'experienced' and 'novice' raters.

Discussion

In this article, we report the design of the fourth version of the CADESI and the evaluation of its validity, reliability and responsiveness (i.e. sensitivity to change), as well as the time required to administer it. Furthermore, we also determined benchmarks for increasing severity of canine AD using receiver operating characteristic methodology.

As for the three preceding versions of this scale,^{3-5,7} the CADESI-4 also assesses the severity of different skin lesions at different body sites. While the CADESI-3 evaluated the severity of four skin lesions, the CADESI-4 reverts to three, like the CADESI-1 and CADESI-2.³⁻⁵ The CADESI-4 assesses the same acute (i.e. erythema) and chronic skin lesions (i.e. lichenification) as in the first three versions. However, whilst the CADESI-3 individually scored two lesions as manifestations of self-trauma (i.e. excoriations and self-induced alopecia), these are now combined in the CADESI-4. Moreover, as it is sometimes difficult to determine whether hair loss is secondary to pruritus, we removed the qualifying adjective 'self-induced' for alopecia. The severity rating for each lesion reverted to that of the first two versions (i.e. four versus six severity grades).

In the first three versions of the CADESI, investigators scored skin lesions over the entire body, which was then divided into an increasing number of areas with each successive modification,^{3-5,7} but this resulted in ever-increasing scoring times. Furthermore, the need to score body areas that are rarely affected in canine AD (e.g. dorsum and head) not only increased the evaluation time unnecessarily, but also yielded CADESI scores that clustered in the low range of the scale.

In the CADESI-4, as in the CADLI,⁹ skin lesions are now mainly scored in areas classically affected in canine AD.¹⁰ The number of sites graded in this new iteration of the scale is 20, compared with 40 in the CADESI-2 and 62 in the CADESI-3.^{4,5,7} Even though the CADESI-1 included only 23 sites, they were distributed over the entire body. The fact that the sites now assessed are those typically affected in dogs with AD increases the probability that a wider range of CADESI-4 values will then be graded in atopic dogs. This assertion is supported by data from this study; for example, in the 31 dogs with active AD the highest value reached in a dog was 61% of the maximal possible score of the CADESI-4 compared with 37% of that of the CADESI-3.

In this study, the validity (i.e. content, construct and criterion) of the CADESI-4 was deemed satisfactory, as shown for both CADESI-3⁷ and CADLI.⁹

The CADESI-4 used the body sites with the highest sensitivity and specificity for the diagnosis of AD, as shown in a large case study.¹⁰ The selection of lesions and severity grades was made from those employed in previous versions of the CADESI and the CADLI. The design of this scale was approved by a majority vote of ICADA members. This committee is composed of veterinarians with a scholarly interest and a track record in canine AD, ensuring that the content of the CADESI-4 was based on 'expert' acceptance.

While the evaluation of the construct of CADESI-3 and CADLI was based on the correlation of the lesional scores

with a scale evaluating pruritus in the same dog, we chose not to do this for the CADESI-4 because a recent study showed that erythema and pruritus do not always evolve in parallel in dogs with AD.² Instead, we found that the CADESI-4 values correlated significantly with those of the two previously validated scales (CADESI-3 and CADLI) with very high correlation coefficients (0.86 in both cases); this agreement with previously validated scales assessing the same disease manifestations satisfied the validation of the CADESI-4 construct.

As for the CADESI-3⁷ and the POEM (a recent scale validated for human AD evaluation),¹³ and in the absence of a gold standard to measure the severity of canine AD, we validated the criterion of the CADESI-4 by correlating the scores with subjective owner and investigator global assessments of lesion severity. The CADESI-4 had higher correlation coefficients with both global assessments of severity than the CADESI-3,⁷ suggesting improvement over the previous version.

The interobserver reliability was assessed both by two clinicians scoring the CADESI-4 on the same dog within an hour of each other and by having five dogs graded by six different veterinarians, most of whom had never used the scale before. The significant correlations – as well as lack of significant difference – between the assessed CADESI-4 value pairs validated the interobserver reliability of this scale. Likewise, the near-perfect correlation and lack of significant difference between two CADESI-4 values assessed by the same clinician at least 3 h apart satisfied its intra-observer reliability. However, because the intra-observer reliability was higher than the interobserver reliability, we recommend that the same investigator scores the CADESI-4 at different visits during clinical trials. If different clinician ratings are necessary, we advise that all investigators should be trained thoroughly in the use of this scale using the provided photographic atlas (see Tables S1 and S2 and Figure S1 in Supplementary material) and that a pretrial scoring phase of multiple dogs by all clinicians be made.

Charman and colleagues recommended that AD measurement scales be assessed for internal consistency, i.e. by determining whether all components of the scale correlate with each other and with the total score.⁶ However, correlation between the components of a scale could merely represent internal redundancy.⁶ While the CADESI-3 had not been assessed for internal consistency,⁷ the total score and components of the CADLI were reported to be fairly consistent.⁹ We found herein that all components of the CADESI-4 correlated with each other, and even more so with the total score. Furthermore, Cronbach's α coefficient calculation was suggestive of a good internal consistency. Altogether, these two methods validated this parameter for the CADESI-4. The fact that the scores for erythema were about twice those for lichenification and excoriation/alopecia is desirable in clinical trials, because erythema should be more responsive to short-term anti-allergic interventions than the other assessed lesions. On the one hand, one could argue that the significant correlations existing between lesion scores should call for a reduction in the number of lesions to grade. On the other hand, the lesions scored are likely to represent different disease stages and/or are

due to different mechanisms of development. As a result, we prefer to keep the lesion combination proposed herein.

For the evaluation of the sensitivity to change of the CADESI-4, we used a methodology different from that for the CADESI-3⁷ and the CADLI.⁹ After transformation into a categorical scale, the percentage change of the CADESI-4 after treatment was significantly correlated with subjective global assessments of treatment efficacy by both owner and clinician. This established that the CADESI-4 had an adequate sensitivity to change.

The time needed to administer the CADESI-4 offers a noticeable improvement over the preceding version. The longest time required to rate a CADESI-4 corresponded to the shortest time taken to grade a CADESI-3 (i.e. 6 min). The median CADESI-4 rating time (4 min) was one-third that of the CADESI-3. However, the simpler design of the CADLI made it quicker to use than the CADESI-4. Surprisingly, CADESI-4 scoring times did not correlate with the total score, i.e. it was equally quick to assess mild AD or severe AD. Nevertheless, clinicians who were less experienced with this scale needed more time than experienced raters. While the median time to grade the scale was only 1 min longer for novice than experienced raters, the former showed much more variation in the time to administer it. We therefore recommend the training of investigators to use this scale using the provided lesion atlas and trial runs with patients before clinical trial onset.

We determined CADESI-4 thresholds separating dogs of increasing AD severity using receiver operating characteristic methodology, as done for both CADESI-3⁷ and CADLI.⁹ The proposed benchmarks separating normal/remission from mild, moderate and severe AD are 10, 35 and 60, respectively. While dogs without AD (i.e. normal dogs) exhibited uniform and tightly bound minimal CADESI-4 values, there was a small overlap between scores of adjacent AD severity categories. Such overlap is to be expected, because both clinicians and owners rated the severity of the disease subjectively and globally without looking at, or taking into account, individual lesions present at the various body sites used for scoring the CADESI-4. Furthermore, and in spite of being instructed not take this into account, owners and clinicians could have been influenced by the severity of pruritus; the pruritus might have been more or less severe than existing skin lesions, leading some owners or clinicians to grade a disease severity higher or lower than if only the skin lesions were examined. In spite of this limitation, these benchmarks should help to homogenize disease severity among atopic dogs enrolled in clinical trials testing the efficacy of therapeutic interventions.

In conclusion, we report the design and validation of the fourth version of the CADESI. This updated version exhibits adequate validity and reliability. The CADESI-4 has many fewer body sites to evaluate than its preceding version; sites are now restricted to those commonly affected in AD. Due in part to this reduction in body areas, it takes only one-third of the time, on average, to score a CADESI-4 compared with a CADESI-3.

The use of 'modified CADESI or mCADESI' scales, be it by changing the number or location of body sites, number or type of lesions or severity grades, should be dis-

couraged. Indeed, any modification of the CADESI-4 voids the validation of the scale and misleads readers. While it is the prerogative of any investigator to design and use their own disease severity scale, it would be deceiving to use a name that contains the acronym CADESI. This should be born in mind by readers, reviewers and journal editors when considering papers containing such terminology.

At this time, the ICADA recommends the use of either CADESI-4 or CADLI as the only two severity scales validated, in unmodified form, to grade skin lesions of dogs with AD. If investigators wish to include a larger number of body sites and a four-point categorical scale, they should select the CADESI-4. If shorter and quicker assessment is required, but with a six-point scale, then the CADLI would be preferable.

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Supporting Information

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

Table S1. CADESI-4 grading sheet (Microsoft® Word® formatted).

Table S2. CADESI-4 grading sheet (Microsoft® Excel® formatted).

Figure S1. CADESI-4 lesion grading atlas (Microsoft® Word® formatted).

Résumé

Contexte Les échelles de sévérité sont utilisées pour grader les lésions cliniques des chiens atopiques (AD) enrôlés dans les essais cliniques. A ce jour, seulement deux échelles ont été validées, le CADESI-3 (Canine Atopic Dermatitis Extent and Severity Index) et le CADLI (Canine Atopic Dermatitis Lesion Index). Cependant, le nombre élevé de sites évalués rend le CADESI-3 inutilisable.

Hypothèses/Objectifs Le but de cette étude était de développer et de valider une quatrième version du CADESI, plus simple et plus rapide à utiliser.

Méthodes Les zones du corps, les lésions et les grades de sévérité ont été revus par les membres de l'ICADA (International Committee on Allergic Diseases of Animals). Le nouveau CADESI-4 a été testé pour sa validité (i.e. contenu, construction et critères), sa fiabilité (i.e. fiabilité inter- et intra-observateur et la consistance interne), la réactivité (i.e. sensibilité au changement) et le temps de réalisation. Les critères de sévérité de la maladie ont été choisis à l'aide de la méthodologie caractéristique de fonctionnement du receveur.

Résultats Le CADESI-4 a été simplifié en comparaison de ses versions précédentes afin de ne considérer que 20 zones corporelles typiquement atteintes chez les chiens atopiques. Trois lésions (érythème, lichénification et alopecie/excoriation) ont été notés de 0 à 3 à chaque site. Le CADESI-4 a une validité, une fiabilité et une sensibilité au changement satisfaisantes. En moyenne, le temps de réalisation du CADESI-4 était d'un tiers celui du CADESI-3. Les critères proposés pour les lésions cutanées d'AD faibles, modérées et sévères sont respectivement 10, 35 et 60.

Conclusions et importance clinique LE CADESI-4 est simple d'utilisation et plus rapide à réaliser que ses versions précédentes. L'ICADA recommande le CADESI-4 au lieu du CADESI-3 pour l'évaluation des lésions d'AD chez les chiens atopiques enrôlés dans les essais cliniques.

Resumen

Introducción las escalas de severidad se usan para valorar las lesiones de la piel en los ensayos clínicos para el tratamiento de perros con dermatitis atópica (AD). En este momento tan solo dos escalas han sido validadas, el índice de extensión y severidad de la dermatitis atópica canina (CADESI)-3 y el índice de lesiones de dermatitis atópica canina (CADLI). Sin embargo el alto número de zonas evaluadas convierte al CADESI-3 en poco práctico.

Hipótesis/Objetivos el propósito de este estudio fue desarrollar y validar la cuarta versión de CADESI que es más sencilla y de mas rápida aplicación.

Métodos las zonas de la piel, las lesiones y la severidad fueron revisados por miembros del Comité Internacional de enfermedades alérgicas en animales (ICADA). El CADESI-4 de nuevo diseño fue examinado para validez (contenido, construcción y criterio), fiabilidad (fiabilidad interna y entre observadores y consistencia), respuesta (sensibilidad al cambio) y tiempo que tarda en aplicarse. Las cotas de severidad se eligieron utilizando metodología de características de operación según receptor.

Resultados el CADESI-4 se simplificó en comparación con su predecesor para incluir 20 sitios que se afectan con frecuencia en perros atópicos. Tres tipos de lesión (eritema, liquenificación y alopecia/excoriación) se evaluaron entre 0-3 para cada zona. El CADESI-4 tuvo validez, fiabilidad y sensibilidad al cambio satisfactorias. De media, el tiempo invertido en la aplicación del nuevo índice fue de un tercio del anterior CADESI-3. Los cotas de puntuación propuestas para lesiones leves, moderadas y severas fueron 10, 35 y 60, respectivamente.

Conclusiones e importancia clínica el CADESI-4 es más simple de utilizar y más rápido de aplicar comparado con la versión previa. El ICADA recomienda CADESI-4 en vez de CADESI-3 para evaluar la lesiones de la piel en perros incluidos en ensayos clínicos.

Zusammenfassung

Hintergrund Die Skalen der Schweregrade werden verwendet, um Hautveränderungen in klinischen Versuchen zur Behandlung von Hunden mit atopischer Dermatitis (AD) zu beurteilen. Zurzeit sind nur zwei Skalen validiert worden, nämlich die Canine Atopic Dermatitis Extent und Severity Index (CADESI)-3 und die Canine Atopic Dermatitis Lesion Index (CADLI). Die hohe Anzahl der beurteilten Körperstellen macht jedoch die CADESI-3 unpraktisch.

Hypothese/Ziele Das Ziel dieser Studie war es, eine vierte Version des CADESI zu entwickeln und zu validieren, die einfacher und schneller zu verwenden ist.

Methoden Die Körperstellen, die Veränderungen und die Schweregrade wurden von Mitgliedern des International Committee on Allergic Diseases of Animals (ICADA) durchgesehen. Der neu entwickelte CADESI-4 wurde auf seine Validität (i.e. Inhalt, Aufbau und Kriterien), die Verlässlichkeit (i.e. inter- und intra-Verlässlichkeit der Ermittler und interne Beständigkeit), die Empfindlichkeit (i.e. Sensitivität auf Veränderung) und Zeitdauer der Anwendung getestet. Benchmarks für die Schwere der Erkrankung wurden mittels Receiver Operating Characteristic Methodologie ermittelt.

Ergebnisse Der CADESI-4 wurde im Vergleich zur früheren Version vereinfacht und umfasst 20 Körperstellen, die typischerweise bei Hunden mit atopischer Dermatitis betroffen sind. Drei Läsionen (Erythem, Lichenifikation und Alopezie/Exkoriation) wurden an jeder Körperstelle von 0 bis 3 beurteilt. Der CADESI-4 hatte eine zufriedenstellende Validität, Verlässlichkeit und Sensitivität in Bezug auf Veränderungen. Durchschnittlich betrug die Zeit zur Anwendung des CADESI-4 ein Drittel der Zeit von CADESI-3. Die vorgeschlagenen Benchmarks für milde, moderate bzw. schwere AD Hautveränderungen lagen bei 10, 35 bzw. 60.

Schlussfolgerungen und klinische Bedeutung Der CADESI-4 ist einfacher und schneller anzuwenden als die frühere Version. Die ICADA empfiehlt die CADESI-4 Version statt wie bisher die CADESI-3 Version zur Beurteilung von Hautveränderungen von AD bei Hunden in klinischen Studien.

要約

背景 – 重症度スコアはアトピー性皮膚炎 (AD) のイヌの治療での臨床治験において皮膚病変を格付けするのに使用されている。現時点では2つの基準、すなわちCanine Atopic Dermatitis Extent and Severity Index (CADESI)-3ならびにCanine Atopic Dermatitis Lesion Index (CADLI) が有効とされている。しかし、評価部位が多いことから、CADESI-3の実行は困難になっている。

仮説/目的 – この研究の目的は、より単純で素早く実施できる4つ目バージョンのCADESIを開発および立証することである。

方法 – 身体部位、皮疹ならびに重症度をInternational Committee on Allergic Diseases of Animals (ICADA) のメンバーにより見直した。新しく考案したCADESI-4を妥当性 (例えば、内容、構成、基準)、信頼性 (例えば、観察者間、観察者内信頼度および内部整合性)、応答性 (例えば、変化による感度) ならびに実施にかかる時間を検査した。疾患の重症度の基準は受信者動作特性法を用いて選択した。

結果 – CADESI-4はアトピー犬で典型的に罹患する20の身体部位から構成する点で、以前のバージョンと比較し、簡易化された。3種類の病変 (紅斑、苔癬化、脱毛/表皮剥離) はそれぞれの部位で0-3にスコアをつけた。CADESI-4 は十分な妥当性、信頼性、および変化による感度を示していた。CADESI-4を実施する時間は、平均でCADESI-3に要する時間の1/3であった。軽度、中等度、高度のADの皮膚病変として提案された基準はそれぞれ10、35、60であった。

結論および臨床的な重要性 – CADESI-4は以前のバージョンと比べ使用するのに単純で、より素早く実施できる。ICADAは臨床試験に組み入れるADの犬における皮膚病変のスコア化にCADESI-3の代わりにCADESI-4を推奨する。

摘要

背景 — 在异位性皮炎 (AD) 患犬临床试验的治疗中, 严重程度被用来给皮肤病变评级。这次, 两个评价标准被确认, 也就是犬异位性皮炎严重程度指数 (CADESI-3) 和犬异位性皮炎病变指数 (CADLI)。然而大量的评估位点使得CADESI-3不切实际。

假设/目的 — 本次研究的重点是显示和证实CADESI-4管理起来更简单和有效。

方法 — 动物过敏症 (ICADA) 国际委员会的成员改进了身体位置、病变及严重程度。针对其有效性 (即内容、概念、标准)、可靠性 (即内外观察可靠性和内部统一性)、反映性 (即对变化的敏感度) 和管理时间, 对新设计的CADESI-4进行测试。用受试者工作特征 (roc曲线) 方法学选择疾病严重程度的基准。

结果 — CADESI-4较之前的版本做了简化, 包括20个典型的异位性皮炎患犬的病变位置。将每个位置的三种病变 (红斑、苔藓化和脱毛/抓痕) 分为0-3级。CADESI-4有着令人满意的正确性、可靠性和敏感度。平均下来, 执行CADESI-4的时间是CADESI-3的三分之一。提议轻度、中度、重度异位性皮炎皮肤病变的基准分别是10、35、60。

总结与临床意义 — CADESI-4比之前版本使用起来更简单, 执行起来更快捷。ICADA建议用CADESI-4代替CADESI-3, 来为参加临床研究的异位性皮炎患犬的皮肤病变评级。

CADESI-4 grading sheet

CADESI-04 (ICADA)			Erythema	Lichenification	Excoriations and/or Alopecia	TOTAL
Perilabial Area <i>(left and right combined)</i>		1				
Medial Pinnae <i>(concave pinnae)</i>	Left	2				
	Right	3				
Axillae	Left	4				
	Right	5				
Front Paws <i>(dorsal and palmar sides combined)</i>	Left	6				
	Right	7				
Hind Paws <i>(dorsal and plantar sides combined)</i>	Left	8				
	Right	9				
Cubital Flexor <i>(elbow folds)</i>	Left	10				
	Right	11				
Palmar Metacarpal <i>(from carpal to metacarpal pads)</i>	Left	12				
	Right	13				
Flanks	Left	14				
	Right	15				
Inguinal Areas <i>(groin)</i>	Left	16				
	Right	17				
Abdomen		18				
Perineum <i>(from vulva/scrotum to anus)</i>		19				
Ventral Tail <i>(proximal)</i>		20				
grade each site and each lesion type: <i>none: 0; mild: 1; moderate: 2; severe: 3</i>			TOTAL Score (20 x 3 x 3 = 180)			

CADESI-4 lesion grading atlas

	none (0)	mild (1)	moderate (2)	severe (3)
erythema				
lichenification				
excoriation				
alopecia				