Received: 20 August 2022 | Accepted: 1 March 2023

DOI: 10.1111/vde.13165

Veterinary Dermatology

ORIGINAL ARTICLE

Efficacy of short-term combination of intralymphatic allergen immunotherapy and lokivetmab treatment in canine atopic dermatitis: A double-blinded, controlled, randomised study

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Funding information
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Abstract

Background: Allergen-specific immunotherapy (ASIT) is an effective therapy for canine atopic dermatitis (cAD). Intralymphatic immunotherapy (ILIT) is potentially beneficial in decreasing time to clinical effectiveness.

Objective: To compare clinical efficacy of six monthly ILIT injections combined with three monthly injections of lokivetmab (LVM) with monthly LVM monotherapy at Day (D)168. To monitor dogs treated with ILIT for an additional six months of subcutaneous immunotherapy (SCIT).

Animals: Thirty-six client-owned dogs with cAD.

Materials and Methods: In this double-blinded, randomised study, dogs received either six monthly injections of ILIT combined with three monthly LVM injections (ILIT group) or six monthly LVM injections (LVM group). Monthly evaluations with pruritus Visual Analogue Scale (pVAS), Canine Atopic Dermatitis Extent and Severity Index, 4th iteration (CADESI-04) and medication scores (MS) were undertaken. Owners completed a Quality of Life (QoL) questionnaire. Treatment success was predefined as ≥50% reduction in pVAS and CADESI-04 score ≤ 10. After D168, the ILIT group continued with SCIT until subjective assessment at 12 months.

Results: The treatment benchmark at D168 was achieved by 11.1% of the ILIT group and 11.8% of LVM group. A significant decrease in mean pVAS and CADESI scores was observed in both groups ($p < 0.001$). The ILIT group had a trend towards higher MS compared to LVM. QoL was better in LVM ($p = 0.01$). At 12 months subjective good-to-excellent response in 77.8% of dogs in the ILIT/SCIT group was seen.

Conclusion and Clinical Relevance: The efficacy of this ILIT protocol was comparable with LVM monotherapy at six months. When ILIT was continued with SCIT, a favourable response was seen.

KEYWORDS
allergen-specific immunotherapy, canine atopic dermatitis, intralymphatic immunotherapy, lokivetmab

INTRODUCTION

Canine atopic dermatitis (cAD) is a common allergic skin disease triggered by common environmental allergens such as house dust mites (HDM) and pollens. In the majority of dogs, the onset occurs at a young age and causes discomfort throughout life for the animal and distress for the owner. Therefore, many anti-inflammatory and anti-pruritic therapies have been developed for the treatment of cAD. Commonly used drugs such as prednisolone, ciclosporin, oclacitinib and lokivetmab each have their pros and cons regarding effectiveness, adverse effects and costs.[1–7] Owners are becoming more aware of possible adverse effects and prefer therapies with the fewest of these. The anti-canine interleukin (IL)-31 monoclonal antibody lokivetmab (LVM) is one of the most specific therapies with very few adverse effects.[6,7] Furthermore, after 28 days of treatment, in comparison to oral ciclosporin, the efficacy in reducing both pruritus and skin lesion scores

was shown to be non-inferior.[6] The initial anti-pruritic response to LVM was shown to be rapid and reduced the pruritus Visual Analogue Scale (pVAS) by >50% in 77% of atopic dogs. However, the overall clinical efficacy of LVM after nine months of treatment was found to be 59%.[6,7] Although LVM is considered a fast-acting and safe treatment for use in atopic dogs, the high costs can limit its use as a maintenance therapy in dogs affected with cAD.

Allergen-specific immunotherapy (ASIT) is the only effective disease-modifying therapy, which changes the hyper-responsive immune system reaction to environmental allergens without further suppressing it. In human medicine, data on the mode of action (MoA) and efficacy mostly is associated with allergic rhinitis and asthma. In humans, the mechanism behind ASIT includes the induction of allergen-specific regulatory T (Treg) cells and their cytokines, induction of allergen-specific immunoglobulin (Ig)G4 concentrations and reduction of both the ratio of Th2/Th1 cytokines and serum allergen-specific IgE.[8–10] In dogs, similar findings have been shown including an increase of Treg cells in peripheral blood[11,12] and interleukin (IL)-10 serum concentrations,[11] change in allergen-specific serum IgE and IgG concentrations,[13] and reduction of inflammatory plasma cytokine concentrations.[12]

Allergen-specific immunotherapy (ASIT) typically consists of an induction and a maintenance phase. During the induction phase, the amount of injected allergens is increased gradually until immunological tolerance is reached.[14] In humans the induction phase usually consists of frequent administrations over a course of three to six months.[14] In cAD the induction phase using alum-precipitated subcutaneous allergen-specific immunotherapy (SCIT) is usually three months and thereafter the maintenance dose is administered.[15] Clinical efficacy of SCIT is estimated at 50%–70% in cAD and may take up to nine or 12 months.[15–19] Attempts have been made to increase the efficacy and to decrease the time of onset to clinical effectiveness. In this regard, sublingual immunotherapy, subcutaneous immunotherapy with conjugated immunomodulatory compounds and allergen-specific rush immunotherapy have been studied in atopic dogs.[13,20–22] Of special interest is the relatively new intralymphatic immunotherapy (ILIT). By the delivery of allergens directly to T and B cells in the lymph node, ILIT potentially could shorten the induction phase or time to reach clinical effectiveness. Indeed, in humans with grass pollen-induced rhinoconjunctivitis ILIT showed faster results compared to conventional SCIT.[23]

Recent studies have shown that ILIT is a safe treatment for dogs with cAD.[24–27] Different treatment protocols with both aqueous and alum-precipitated allergens have been used with variable efficacies at various time points.[24–27] Clinical efficacy is not expected to be seen during the induction phase of ASIT in general. Therefore, it would be unethical to leave atopic dogs without supportive medication during this period. Because the MoA of LVM is targeted, it is theoretically a good choice for concurrent treatment during the induction phase of ASIT in dogs with cAD.

Hypothesis and outcome

The aim of this study was to evaluate the clinical efficacy of six monthly ILIT injections combined with three monthly LVM injections during the first three months of ILIT in dogs with cAD. The efficacy of this ILIT protocol was compared with LVM monotherapy after six months of treatment in nonseasonal atopic dogs. Additionally, allergen immunotherapy for dogs in the ILIT group was continued as SCIT after Day (D)168 during an open-label follow-up period for an additional six months. Clinical efficacy during the follow-up was determined by owners' and clinicians' subjective assessment of clinical improvement, and assessment of concurrent systemic medications after a total of 12 months of immunotherapy.

The clinical efficacies of the ILIT/LVM protocol and LVM monotherapy were evaluated at D168 using outcome measurements Canine Atopic Dermatitis Extent and Severity Index, 4th iteration (CADESI-04)[28] and pVAS[29] scores. Secondary outcome measurements were medication score (MS)[30] and Quality of Life (QoL).[31] It was hypothesised that the clinical efficacy after six months of treatment of alum-precipitated ILIT in combination with three monthly LVM injections during the first three months would be comparable to LVM monotherapy.

MATERIALS AND METHODS

Ethics

Animals were randomised to two standard-of-care arms and placebo (saline) injections were considered to be no greater than minimal risk by the investigators' institution. Therefore, the usual requirements for formal institutional approval were waived by IVC Evidensia, Netherlands. Owners signed a consent form after thorough written and oral explanation of the treatment and study.

Study dogs

Client-owned dogs diagnosed with nonseasonal cAD were included in this study. Canine AD was diagnosed based on published clinical criteria[32] and ruling out appropriate differential diagnoses. For all dogs, food-induced atopic dermatitis (FIAD) was diagnosed with an elimination diet trial for a minimum of six weeks followed by challenge before inclusion in this study. Dogs with FIAD were included, as for all dogs no dietary changes were allowed during the study. Dogs previously treated with any form of ASIT were excluded from study participation. Preventive flea treatment

during the trial was mandatory for all dogs, starting one month before the start of the trial.

Inclusion criteria

The following inclusion criteria were used: perennial clinical signs, minimum age of 12 months, weight in the range of 3–80 kg and good overall health.

In order to qualify for enrolment in the study, cut-off criteria for the primary outcome measurements at study intake were predetermined with the requirement of a minimum CADESI-04 score of 35 or pVAS score of six. Withdrawal times for prohibited medications before the start of the trial were two weeks for live vaccines, topical glucocorticosteroids, oclacitinib, antihistamines, oral antibiotics and antifungals, four weeks for topical tacrolimus, oral glucocorticosteroids and oral ciclosporin, six weeks for long-acting injectable glucocorticosteroids, and 12 weeks for LVM. At least two weeks before the start of the trial and study intake, topical antimicrobial treatment had to be reduced to once weekly.

Allergen testing

In all dogs, allergen testing was performed by intradermal (Artuvetrin allergens; Nextmune) and IgE serological tests (Next+ Serum Test; Nextmune). Only dogs with at least a positive result for HDM (*Dermatophagoides farinae*), one or more storage mites and/or *Malassezia* were included. Positivity to additional allergens was accepted. At the end of the study on D168 allergen-specific serum IgE (AsIgE) measurement was repeated to evaluate potential changes induced by allergen immunotherapy.

Study protocol and clinical evaluation to assess the efficacy of treatment

In this double-blinded study, dogs were randomly assigned to either six monthly injections of ILIT combined with three monthly LVM injections (ILIT group) or six monthly LVM injections (LVM group). Additionally, dogs in the ILIT group were followed up for an additional six months in a nonblinded format while receiving monthly SCIT injections. During the initial clinical trial dogs in the ILIT group received six monthly intralymphatic injections with allergens (Artuvetrin; Nextmune) and six monthly subcutaneous injections of which the first three were LVM (Cytopoint; Zoetis) and the last three saline. Thereafter, allergen immunotherapy with the same allergens was continued as monthly SCIT starting from D168. Dogs in the LVM group received six monthly subcutaneous LVM injections and six monthly intralymphatic injections with saline from D0 to D140.

Study dogs were randomly assigned within subgroups of four dogs to either the ILIT or LVM group, and visited the animal hospital for treatment every 28 days (±1–3 days) for six months with a final recheck at D168. The primary outcome measurements pVAS and CADESI-04 were recorded at every visit (visits 1–7). The pVAS was scored in consideration of the 24 h previous to the recheck. The overall study treatment and clinical evaluation protocol is illustrated in Table 1.

Medication was prescribed as required based on the history, pruritus score and presence of skin lesions. Efforts were made to use as little medication as necessary and to minimise the duration of treatment without compromising the dog's welfare. Maintenance therapy to control secondary skin infections and prevent otitis externa included once-weekly use of a topical antimicrobial (shampoo, mousse, spray

TABLE 1 Study protocol of treatment and clinical evaluation of both groups of atopic dogs over time.

Time point	Primary outcome measurements	Secondary outcome measurements	Treatment ILIT group	Treatment LVM group
D0	pVAS CADESI-04	QoL (T0)	ILIT+LVM	LVM
D28	pVAS CADESI-04	MS1	ILIT+LVM	LVM
D56	pVAS CADESI-04	MS2	ILIT+LVM	LVM
D84	pVAS CADESI-04	MS3	ILIT	LVM
D112	pVAS CADESI-04	MS4	ILIT	LVM
D140	pVAS CADESI-04	MS5	ILIT	LVM
D168	pVAS CADESI-04	MS6, QoL (T1)	Continue as SCIT	N/A

Note: During the first three months [Day(D)0–D56] of intralymphatic immunotherapy (ILIT), dogs in the ILIT group also received three monthly injections of lokivetmab (LVM). Primary outcome measurements were pruritus Visual Analogue Scale (pVAS) and skin lesion (Canine Atopic Dermatitis Extent and Severity Index, fourth iteration, CADESI-04) scores at D168 compared to baseline (D0). Secondary outcome measurements were medication scores (MS; 1–6), Quality of Life (QoL; T0–T1) questionnaire and pVAS and CADESI scores for other time points (D28–D140). At the end of the study (D168), measurement of allergen-specific serum immunoglobulin (Ig)E (AsIgE) concentrations was repeated.

Abbreviation: N/A, non-applicable.

or wipes), once-weekly ear cleaning and once-weekly triamcinolone ear medication (acetic acid with triamcinolone acetonide 0.1% or triamcinolone ointment 0.1%). The use of concurrent therapy was recorded for each dog by the owner in monthly schedules (MS 1 to 6) and graded using a modified version of a previously reported validated MS (see Table S1).[30] In order to assess a correlation of the used concurrent medications with pVAS or CADESI scores, the MS was divided into low score (<10) and high score (>10). At D0 and D168, the same owners filled in a validated QoL questionnaire,[31] pertaining to the previous week. The questionnaire consisted of 15 questions, which were subdivided into one general question on the severity of the disease and clinical signs (QoLS, Q1), seven questions on QoL of the dog (QoL1, Q2–8) and seven questions on QoL of the owner (QoL2, Q9–15). For each question, a score of 0–3 could be achieved. If owners ticked two answers per question, the mean of these two values was taken.

To address the long-term clinical efficacy of ILIT/SCIT, dogs in the ILIT group were included in an open-label follow-up period of up to 12 months of therapy. To optimise therapy, one or more rechecks were performed by the institutional clinicians in the period between six and 12 months. The end-point was a subjective assessment by both the owner and clinician regarding the clinical improvement and use of concurrent systemic medication.

Treatment protocol

The allergens for ILIT were selected based on the history and results of serological and intradermal tests. For some dogs seasonal allergens were added to immunotherapy when a causal relation could not be excluded, despite their nonseasonal clinical signs. For optimal results, intralymphatic injections of 0.2 mL were administered under ultrasound guidance (HS40; Samsung Medison Co. Ltd) and injections into alternate popliteal lymph nodes were performed. Before ultrasound-guided injections, hairs were clipped if necessary and skin was disinfected with alcohol spray. After the administration of treatment, owners and their dogs were asked to stay in the animal hospital for 1 h to monitor for acute adverse effects.

The LVM dose ranged from 1.0 to 2.2 mg/kg body weight (medians of 1.2 mg/kg for the ILIT group, and 1.25 mg/kg for the LVM group) and was given subcutaneously.

From the start of therapy and at every recheck up to D140, each dog received an injection into a lymph node and a subcutaneous injection of 1.0 mL for dogs <40 kg or 2.0 mL for dogs >40 kg. Sterile saline was used subcutaneously in the ILIT group and intralymphatically in the LVM group. In case a dog would need to receive two injections of ILIT (>8 allergens), two injections of saline (0.2 mL) were given (one in each popliteal lymph node) when assigned to the LVM group to guarantee double-blindness. All syringes were taped to guarantee the blindness of the investigators.

After D168, ILIT-treated dogs received six monthly SCIT injections of 1.0 mL or a volume adjusted to individual needs.

Assessment of efficacy of treatment

The primary outcome measurements of successful treatment on D168 were predefined as ≥50% reduction in pVAS compared to D0 and a CADESI-04 score ≤ 10. Secondary outcome measurements included MS, QoL, and pVAS and CADESI scores at each time point during the study. Two weeks before the last recheck at D168, concurrent systemic treatment was prohibited.

Additionally, long-term treatment efficacy of ILIT/SCIT was determined 12 months after the start of the study by the owners' and clinicians' subjective assessment of the improvement in clinical signs and the concurrent use of systemic medication. Treatment success was defined as poor (<50% clinical improvement and no reduction of systemic medication), good (≥50% clinical improvement with or without reduction of systemic medication) or excellent (controlled with ASIT alone).[16]

Withdrawal criteria

Dogs were withdrawn from study participation when either welfare or health conditions would be compromised, on request by the pet owner or as a result of lack of owner compliance.

Statistical analyses

Data were entered in EXCEL (Microsoft) and exported to the statistical program R v4.0.5 (R Core Team) via the *library readxl* package v.1.4.0. Libraries *ggplot2*[33] and *psych*[34] were used to visualise and summarise the data. Difference in mean baseline scores for CADESI-04, pVAS, QoL1, QoL2 and MS, respectively, between treatment groups was tested with the independent Student's *t*-test. The outcomes CADESI-04 and pVAS were analysed with a linear mixed effects model,[35] with the factors of time, treatment (ILIT or LVM), MS and the interaction term between time and treatment as explanatory variables assuming a normal distribution. To account for repeated observations, a random effect for dog identification was added to the model. The Akaike information criterion was used to select the best model in a backward selection approach. Time and treatment remained in the model at all times to answer the research questions. Visual inspection of the residuals was applied for model validity and no aberrations were observed. The MS was analysed in a similar approach with the factors of time, treatment and the interaction between both groups and MS was log-transformed to meet the model assumptions, although homoscedasticity was not completely fulfilled. To avoid the effect of a very high MS (>15) in the first

month of the study (MS1), we also applied the previously assessed final models for CADESI-04, pVAS and MS only with data of dogs with MS1 < 15, and studied the differences in estimates based on the full data. The reporting guidelines of CONSORT were used to report this study.[36] A p-value of <0.05 was chosen to indicate statistical significance.

RESULTS

A total of 36 dogs with nonseasonal AD fulfilled the inclusion criteria and were included in this study. Thirty-five dogs completed the study and were included in the statistical analyses, resulting in 18 dogs in the ILIT group and 17 dogs in the LVM group. There was one dropout in the ILIT group owing to the development of neurological signs consistent with meningitis. Twenty-two dog breeds were represented of which the following were most common: cross-breed ($n=9$), German Shepherd dogs- ($n=3$), French bulldog ($n=2$), West Highland white terrier ($n=2$), white Swiss shepherd dog ($n=2$) and Dachshund ($n=2$). Of the remaining dogs, there was only one dog per breed. The average age at the start of the study was three years (range 1–7 years) with a mean age of onset of clinical signs of 1.4 years (range 0.5–6 years). Numbers of females and males in the study were equal with nine males in both groups, 10 females in the ILIT group and eight in the LVM group.

Baseline scores at D0 for pVAS, CADESI and QoL, and MS1 at D28 did not differ significantly between the two groups (pVAS, $p=0.45$; CADESI, $p=0.55$; QoLS, $p=0.94$; QoL1, $p=0.67$; QoL2, $p=0.06$; MS1, $p=0.20$). Intralymphatic injections were well-tolerated by all dogs. Very few mild adverse effects of ILIT were seen, which included mild enlargement of popliteal lymph nodes, occasional gastrointestinal signs (e.g. hyporexia, vomiting, diarrhoea), mild increase in pruritus, and lethargy, all of which were of short duration (few days) and self-limiting.

Data was available from the unblinded, uncontrolled follow-up part 12 months after study initiation for 17 of 18 dogs in the ILIT group. One dog with a good response after nine months of ILIT/SCIT was lost to follow-up at 12 months.

Clinical evaluation

In both groups, mean pVAS and CADESI-04 values were lower at each measured time point compared to D0, with no significant differences between the groups. (Table 2 and Tables S2 and S3; Figure 1a–d). However, the change over time in mean pVAS and CADESI scores was significant in both groups ($p<0.001$). Based on the predefined criteria of ≥50% reduction in pVAS at D168 compared to D0 and a CADESI-04 score ≤ 10, treatment was successful in two of 18 dogs (11.1%) in the ILIT group and in two of 17 dogs (11.7%) in the LVM group. For these dogs, the MS remained zero or decreased by ≥50%. Using different cut-off values higher treatment efficacy was seen with the exception of pVAS ≤2 cm for dogs in the ILIT group (Table 3). A ≥50% improvement in pVAS and CADESI-04 scores at D168 was observed in 16.7% of the ILIT group and 29.4% of the LVM group. In these dogs, the MS remained stable or decreased.

During the study, an increase in the mean MS was seen. For the LVM group, the largest difference in mean MS compared to MS1 was observed at month six (+48%) (Table S4). On average, over time, dogs in the ILIT group had a higher MS (65%) compared to dogs in the LVM group (Table 2 and Table S4; Figure 1e,f), although this was not significant. Dogs with high MS (>10) had a tendency towards a higher CADESI-04 score (8.8 points) compared to dogs with a low MS in both groups, whereas this was less obvious for the pVAS values (Figure S1). Seventeen of 35 dogs (48.6%) required no additional systemic therapy during the entire study, of which were seven in the ILIT and 10 in the LVM group.

Mean QoLS, QoL1 and QoL2 in both groups were lower at D168 compared to D0 (Table 2) with no significant difference in QoLS decrease between both groups ($p=0.51$). However, the QoL1 decreased significantly ($p=0.01$) more in the LVM group (−4.66) than in the ILIT group (−0.62) (Figure S2). In addition, a significant difference between the groups for two individual questions concerning disturbance of the dog's sleep and playing or working activities (Q3, $p=0.05$ versus Q5, $p=0.01$), also was seen in favour of the LVM group (Figure S2). The change in QoL2 from D0 to D168 between the LVM and ILIT group did not differ ($p=0.46$). The findings were similar when dogs with very high MS (>15) in the first month were excluded (results not shown).

After 12 months in the ILIT/SCIT group, three of 18 dogs showed poor response, eight of 18 dogs good response and six of 18 dogs excellent response. SCIT was continued in 14 of 18 dogs (77.8%).

Allergens and immunotherapy

Allergen testing was performed in all 35 dogs, consisting of one intradermal test (IDT) and two allergen-specific IgE serological tests (before start of study and at D168). A total of five dogs in the ILIT group (26.3%) and three in the LVM group (17.6%) had a negative IDT and both groups had one dog with a negative serological test (5.6% in the ILIT group, 5.9% in LVM group). The mean number of allergens administered in ILIT was eight (7.67, range 4–12). An overview of selected allergens from both allergen tests and number of dogs with one or more positive reactions per allergen and treatment group is illustrated in Table S5. When AsIgE results from D168 were compared to those from before the start of the study, both a decrease and increase in serum concentrations of AsIgE were seen for individual dogs in both groups for various allergens (Figure S3). In addition, in both groups, new allergens considered to be positive were seen (mean 2.1 in the ILIT group, 2.4 in the LVM group).

TABLE 2 Mean and standard deviation of primary and secondary outcome measurements per visit for atopic dogs in the intralymphatic immunotherapy (ILIT; $n=18$) and lokivetmab (LVM; $n=17$) groups.

	Day(D)0	D28	D56	D84	D112	D140	D168
pVAS[a]							
ILIT group[c]	6.4 ± 2.1	4.5 ± 2.5	4.7 ± 2.1	4.5 ± 2.1	4.6 ± 2.4	5.6 ± 2.4	5.6 ± 1.9
LVM group	7.4 ± 1.6	3.8 ± 2.6	4.7 ± 2.0	4.3 ± 1.8	4.3 ± 2.4	4.4 ± 2.2	4.6 ± 2.3
CADESI-04[a]							
ILIT group[c]	43.8 ± 15.7	31.6 ± 14.7	28.8 ± 14.2	23.8 ± 11.6	20.1 ± 9.7	24.7 ± 11.8	23.4 ± 13.8
LVM group	46.9 ± 15.1	31.5 ± 13.7	27.2 ± 11.8	24.9 ± 11.5	24.2 ± 12.5	21.8 ± 13.0	23.6 ± 11.8
Medication score							
ILIT group[c]	N/A	6.2 ± 10.0	7.6 ± 10.0	7.6 ± 10.6	9.9 ± 14.9	8.5 ± 10.8	11.9 ± 13.0
LVM group	N/A	2.8 ± 4.0	2.2 ± 3.0	4.1 ± 6.1	4.8 ± 6.1	5.1 ± 7.7	2.9 ± 4.0

QoL	D0	D168
QoLS		
ILIT group	2.2 ± 0.6	1.8 ± 0.8
LVM group	2.2 ± 0.7	1.3 ± 0.8
QoL1[b]		
ILIT group	7.3 ± 4.5	6.4 ± 4.7
LVM group	7.9 ± 3.2	3.6 ± 3.3
QoL2		
ILIT group	7.7 ± 4.1	7.1 ± 4.0
LVM group	7.2 ± 2.8	5.5 ± 3.3

Abbreviations: CADESI-04, Canine Atopic Dermatitis Extent and Severity Index, 4th iteration; pVAS, pruritus Visual Analogue Scale; QoL, quality of life; QoLS, general severity of disease; QoL1, quality of life of dog; QoL2, quality of life of owner.

[a]The change over time in mean pVAS and CADESI-04 scores was significant in both groups ($p<0.001$).

[b]significant difference LVM treated dogs compared to ILIT group at D168 compared to D0 ($p=0.01$).

[c]In the ILIT group, a combination of ILIT and LVM during the first three months was used (D0–D56).

DISCUSSION

In this study, the clinical efficacy of an ILIT protocol combined with three monthly administrations of LVM was evaluated after six months of treatment and compared with six monthly treatments with LVM. We found that the two treatment regimes were comparable at D168. After 12 months of ILIT/SCIT therapy, 14 dogs from this treatment group were considered to have a good-to-excellent response and treatment was continued. Comparing the pruritus and clinical lesion scores of each group at D168 an improvement was seen in four dogs, two from each group (11%), using our predefined criteria. These are lower success rates than expected based on previously published studies.[6,7,14–16,25–27] This may be the result of the more stringent predefined outcome measurements used in our study. When the success of treatment was determined using less stringent criteria, clinical efficacy would have been higher in both groups (Table 3). If analysing the CADESI scores only in our study, 61.1% of ILIT dogs showed ≥50% reduction at D168 compared to 52.9% of LVM dogs. A similar result of ILIT-treated dogs was seen at D360 in a previous study showing ≥50% reduction of CADESI-03 in 66.7%, it should be noted that this was a longer study and a previous iteration of the CADESI score was used.[26] When only assessing pruritus at D168 compared to D), ≥50% reduction of pVAS there was a better response in the dogs treated with LVM only;16.7% ILIT group, 35.3% of LVM group (Table 3).

An explanation for the lower efficacy of LVM in our study may be the lower LVM dose of 1.0 mg/kg (licensed European dose) used compared to other published studies (2.0 mg/kg, licensed United States dose).[7,37] In one study using a comparable dose of 1.0 mg/kg LVM, 64.7% of dogs showed ≥50% reduction of pVAS at D28, which is similar to 58.8% of dogs seen in the LVM group at D28 in our study (Table S6).[38] The even lower percentage of ILIT-treated dogs showing ≥50% decrease in pVAS is likely to have been influenced by the presence of three dogs with a very low pVAS at D0 (range 2.1–3.2), whereas in the LVM group, the lowest pVAS at D0 was 4.2.

Clearly therapeutic success and clinical efficacy can vary with different outcome measurements and is low at D168 in our study for both treatments. With regard to the ILIT group, this is likely to be the short duration of six months and it is generally considered that a 12-month period is optimal. This is a limitation of our study. However, other ILIT studies have shown improvement in clinical scores within three to six months.[25,26] Moreover, in the study by Mueller et al.[27] significant improvement of total score (skin lesion, pruritus and medication scores) was already seen from one month of treatment.

Another possible explanation for the overall lower effectiveness found in this study is the severity of the disease. Our study contained at inclusion high numbers of dogs classified as having moderate AD based on the CADESI-04 (61.1% for the ILIT group, 70.6% for the

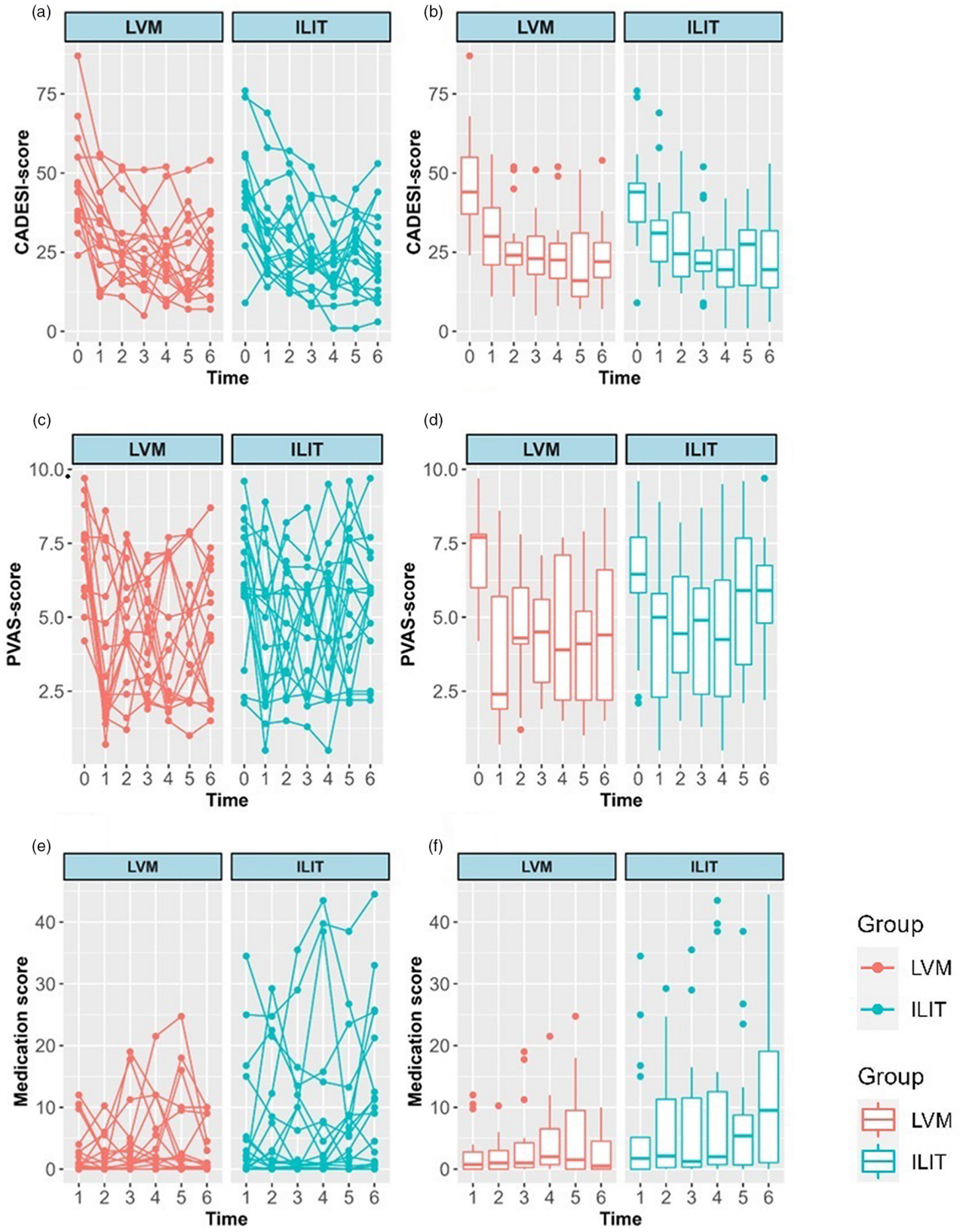

FIGURE 1 Skin lesion (Canine Atopic Dermatitis Extent and Severity Index, 4th iteration, CADESI-04), pruritus (Visual Analogue Scale, pVAS) and medication scores (MS) of individual dogs per treatment group over time. Overview of the change of CADESI-04 (a,b), pVAS (c,d) and MS (e,f) over time in the lokivetmab (LVM; $n = 17$) and intralymphatic immunotherapy (ILIT; $n = 18$) groups. Measurements of CADESI and pVAS were taken before start of treatments at Day (D)0 and every month until D168 (months 0–6). The amount of concurrent medication used within a month was recorded by the owners (MS1-6) where MS1 covers the time period from D0 to D28. The line graphs on the left show the (dis)similarity of individual dogs in course of time with different (starting) levels and difference in changes of each time interval between dogs. These graphs show high variability within each dog over time, especially for pruritus scores (pVAS) with very low within dog correlation. The boxplots on the right illustrate the mean level of scores and variation, the standard deviation (line) and most extreme values (dots) per group for each time point.

TABLE 3 Treatment success for atopic dogs in the intralymphatic immunotherapy (ILIT; $n = 18$) and lokivetmab (LVM; $n = 17$) groups at Day (D)168 comparing different cut-off values.

Treatment success[a] defined as:	≥50% reduction pVAS and CADESI-04 score ≤ 10	≥50% reduction pVAS and CADESI-04	≥50% reduction pVAS, CADESI-04 and MS	≥50% reduction pVAS	pVAS ≤2 cm	CADESI-04 score ≤ 10	≥50% reduction CADESI-04	≥50% reduction of MS
Number of dogs ILIT group:	2/18 (11.1%)	3/18 (16.7%)	3/18 (16.7%)	3/18 (16.7%)	0/18 (0%)	3/18 (16.7%)	11/18 (61.1%)	5/18 (27.8%)
Number of dogs LVM group:	2/17 (11.8%)	5/17 (29.4%)	3/17 (17.6%)	6/17 (35.3%)	2/17 (11.8%)	2/17 (11.8%)	9/17 (52.9%)	9/17 (52.9%)

Note: During the first three months, dogs in the ILIT group also received three monthly injections of LVM.
Abbreviations: CADESI-04, Canine Atopic Dermatitis Extent and Severity Index, 4th iteration; MS, medication score; pVAS, pruritus Visual Analogue Scale.
[a]Treatment success in this study was predefined as ≥50% reduction of pVAS and a CADESI-04 score ≤ 10 at D168 compared to start of study (D0).

LVM group) and having severe AD based on the pVAS (83.3% for the ILIT group, 88.2% for the LVM group). By contrast, most dogs treated with ILIT in previous studies were classified as having mild-to-moderate AD.[25–27]

Another factor contributing to the lower efficacy rate also may be related to more stringent concurrent medication use in this study in combination with more severe disease. Just enough systemic medication was given to keep clinical signs ethically acceptable without the reduction of pVAS and CADESI values to normal levels (Figure S1). In almost 50% of dogs in this study, no concurrent systemic medications were used. This may have affected the QoL scores in the ILIT group in a negative way as mostly more intensive topical therapy was needed. However, the more severely affected animals with high pVAS and/or CADESI-04 scores received systemic intervention therapy. Despite the increase of the mean MS in both groups, a ≥50% reduction of MS in 27.8% for the ILIT group and 52.9% for the LVM group was seen after six months (Table 3). Another reason possibly attributing to the found difference in QoL might be that two owners in the ILIT group did not fill in the entire questionnaire at D168 and were, therefore, excluded in the analysis (per protocol analysis).

There was a high variability in pVAS and CADESI scores for the individual dogs over time in both groups (Figure 1). When the data were assessed, no obvious seasonal effects were observed. However, owing to the short duration of the study, a seasonal influence could have been missed despite the included dogs being affected all year.

In our study, the pVAS related to the degree of pruritus 24 h before the visit. In a recent study, a correlation between the mean pruritus scores in the last seven and 30 days before the visit was seen.[27] Possibly the use of a mean value of seven days before the visit would have been better.

Of interest was the finding of a change in AsIgE levels over time in both groups. Thorough evaluation of the data, including seasonal influences, did not provide an explanation for all the changes found. Within the duration of this study, no changes induced by ILIT measured by serum AsIgE could be found. Repeated measurements over a year or more are likely to be required to better assess changes in AsIgE[11,39] However, in a six-month trial of SLIT a decrease in median serum IgE of *D. farinae* and increase of median serum IgG concentrations was seen.[13] Use of LVM over a six-month period (in the LVM group) may have resulted in a decrease in AsIgE concentrations. A recent study reported a slight reduction in AsIgE associated with LVM use; however, the dose used was higher (median 2.37 mg/kg) than that used in our study and in some cases the duration of therapy was longer (median four weeks; range 1–140 weeks).[40]

In this study, the used protocol combining ILIT with LVM was found to be a safe therapy for atopic dogs. Although results of this ILIT protocol were comparable with LVM monotherapy in this study, we were not able to show an advantage over other ILIT protocols used in other studies.[24–27] However, a substantial further improvement was seen after 12 months of ILIT/SCIT.

Allergen immunotherapy was continued in 77.8% of the dogs based on subjective assessment of clinical improvement by the owners and clinician. This assessment method has been used in previous studies in which clinical improvement often is defined as >50% reduction of clinical signs.[15–18] The failure to continue with validated scores for pruritus, skin lesions and medication in the LVM/SCIT group is a major limitation.

Hence, more double-blinded, controlled, longer-duration studies with higher numbers of dogs are needed to determine optimal ILIT protocols (e.g. frequency, dose and duration). Further research is needed to determine if anti-IL-31 monoclonal antibody therapy can improve ASIT efficacy in the longer term in standardised studies concerning the use of concurrent medication with validated medication scores.

In conclusion, ILIT combined with three monthly LVM injections was found to be a safe therapy with comparable efficacy after six months compared to LVM monotherapy. Future studies with longer follow-up periods using validated scores and larger numbers of dogs are needed to discover whether the efficacy of the ILIT protocol used here might improve further over time.

AUTHOR CONTRIBUTIONS

Kelly van Amersfort involved in conceptualisation, visualisation, writing the original draft, project administration, investigation, review and editing. **Johannes C.M. Vernooij** involved in methodology, formal analysis, visualisation, review and editing and data curation. **Annette van der Lee** involved in conceptualisation, supervision, visualisation, investigation, writing the original draft, review & editing, project administration and funding acquisition.

ACKNOWLEDGEMENTS

We would like to thank our veterinary nurse Mrs Jolein Boekhoven for supporting us in conducting and organising the practical part of the study.

FUNDING INFORMATION

This study was partly funded by Nextmune, Lelystad, The Netherlands.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: van Amersfort K, Vernooij JCM, van der Lee A. Efficacy of short-term combination of intralymphatic allergen immunotherapy and lokivetmab treatment in canine atopic dermatitis: A double-blinded, controlled, randomised study. Vet Dermatol. 2023;34:373–384. https://doi.org/10.1111/vde.13165

Résumé

Contexte: L'immunothérapie spécifique aux allergènes (ASIT) est une thérapeutique efficace pour la dermatite atopique canine (cAD). L'immunothérapie intralymphatique (ILIT) est potentiellement bénéfique pour réduire le délai d'action clinique.

Objectif: Comparer l'efficacité clinique de six injections mensuelles d'ILIT associées à trois injections mensuelles de lokivetmab (LVM) avec une monothérapie mensuelle de LVM au jour (J)168. Évaluer les chiens traités par ILIT durant six mois supplémentaires d'immunothérapie sous-cutanée (SCIT).

Animaux: Trente-six chiens de clients souffrant de cAD.

Matériels et méthodes: Dans cette étude randomisée en double aveugle, les chiens reçoivent soit six injections mensuelles d'ILIT combinées à trois injections mensuelles de LVM (groupe ILIT), ou six injections mensuelles de LVM (groupe LVM). Des évaluations mensuelles sont effectuées avec l'échelle visuelle analogique du prurit (pVAS), l'indice d'étendue et de sévérité de la dermatite atopique canine, 4e édition (CADESI-04) et les scores de traitement (ST). Un questionnaire de qualité de vie (QoL) est également remis. Un succès thérapeutique est défini comme une réduction ≥50 % de la pVAS et un score CADESI-04 ≤10. Après J168, le groupe ILIT poursuit avec le protocole SCIT jusqu'à l'évaluation subjective à 12 mois

Résultats: Le repère thérapeutique à J168 est atteint par 11,1% des chiens du groupe ILIT et 11,8% du groupe LVM. Une diminution significative des scores pVAS et CADESI moyens est observée dans les deux groupes ($p < 0,001$). Le groupe ILIT avait une tendance à un ST plus élevé par comparaison au LVM. La qualité de vie était meilleure pour le groupe LVM ($p = 0,01$). À 12 mois, une réponse subjective bonne à excellente chez 77,8 % des chiens du groupe ILIT/SCIT a été observée.

Conclusion et pertinence clinique: L'efficacité de ce protocole ILIT est comparable à la monothérapie LVM à six mois. Lorsque ILIT est poursuivi avec SCIT, une réponse favorable est observée.

Resumen

Introducción: la inmunoterapia específica para alérgenos (ASIT) es una terapia eficaz para la dermatitis atópica canina (cAD). La inmunoterapia intralinfática (ILIT) es potencialmente beneficiosa para disminuir el tiempo hasta la efectividad clínica.

Objetivo: comparar la eficacia clínica de seis inyecciones mensuales de ILIT combinadas con tres inyecciones mensuales de lokivetmab (LVM) con monoterapia mensual de LVM en el día (D)168. Monitorear perros tratados con ILIT durante seis meses adicionales de inmunoterapia subcutánea (SCIT).

Animales: Treinta y seis perros de propietarios particulares con AD.

Materiales y métodos: en este estudio al azar, doble ciego, los perros recibieron seis inyecciones mensuales de ILIT combinadas con tres inyecciones mensuales de LVM (grupo ILIT) o seis inyecciones mensuales de LVM (grupo LVM). Se realizaron evaluaciones mensuales con Escala Visual Análoga de Prurito (pVAS), Índice de Severidad y Extensión de Dermatitis Atópica Canina, cuarta revisión (CADESI-04) y valores de medicación (MS). También se administró un cuestionario de calidad de vida (QoL). El éxito se predefinió como una reducción de ≥50 % en pVAS y una puntuación de CADESI-04 ≤10. Después de D168, el grupo ILIT continuó con SCIT hasta la evaluación subjetiva a los 12 meses.

Resultados: El punto de referencia del tratamiento en D168 fue alcanzado por el 11,1 % del grupo ILIT y el 11,8 % del grupo LVM. Se observó una disminución significativa en las puntuaciones medias de pVAS y CADESI en ambos grupos ($p < 0{,}001$). El grupo ILIT tuvo una tendencia hacia una mayor MS en comparación con LVM. QoL fue mejor en el grupo LVM ($p = 0{,}01$). A los 12 meses se observó una respuesta subjetiva de buena a excelente en el 77,8 % de los perros del grupo ILIT/SCIT.

Conclusión y relevancia clínica: la eficacia de este protocolo ILIT fue comparable con la monoterapia con LVM a los seis meses. Cuando ILIT se continuó con SCIT, se observó una respuesta favorable.

Zusammenfassung

Hintergrund: Die Allergen-spezifische Immuntherapie (ASIT) ist eine wirksame Therapie für die atopische Dermatitis (cAD) des Hundes. Die intralymphatische Immuntherapie (ILIT) ist möglicherweise nützlich, um die Zeit bis zur klinischen Wirksamkeit zu reduzieren.

Ziel: Ein Vergleich der klinischen Wirksamkeit von ILIT-Injektionen alle sechs Monate in Kombination mit Injektionen von Lokivetmab (LVM) alle drei Monate mit monatlicher LVM Monotherapie am Tag (D) 168. Das Ziel war es, Hunde, die mit ILIT behandelt worden waren, für weitere sechs Monate, während sie eine subkutane Immuntherapie (SCIT) erhielten, zu beobachten.

Tiere: Sechsunddreißig Hunde mit cAD, die in Privatbesitz waren.

Materialien und Methoden: In dieser doppelt-blinden, randomisierten Studie, erhielten Hunde entweder alle sechs Monate Injektionen von ILIT in Kombination mit LVM-Injektionen alle drei Monate (ILIT Gruppe) oder LVM Injektionen alle sechs Monate (LVM Gruppe). Es wurden monatliche Evaluierungen mittels Pruritus Visual Analog Scale (pVAS), Canine Atopic Dermatitis Extent and Severity Index, 4. Ausgabe (CADESI-04) und medizinische Bewertungen (MS) durchgeführt. Ebenso wurde ein Fragebogen zur Lebensqualität (QoL) eingesetzt. Erfolg wurde vorab definiert als ≥50% Reduzierung der pVAS und CADESI-04 Werte ≤10. Nach dem D168 wurde die ILIT Gruppe mit SCIT bis zu einer subjektiven Bewertung nach 12 Monaten fortgeführt.

Ergebnisse: Der festgelegte Maßstab der Behandlung am D168 wurde von 11,1% der ILIT Gruppe und 11,8% der LVM Gruppe erreicht. Eine signifikante Abnahme der durchschnittlichen pVAS und CADESI Werte wurde in beiden Gruppen beobachtet ($p < 0{,}001$). Die ILIT Gruppe zeigte im Vergleich zu LVM einen Trend zu höheren MS. QoL war bei der LVM Gruppe besser ($p = 0{,}01$). Nach 12 Monaten wurde eine subjektive gute-bis-exzellente Antwort bei 77,8% der Hunde in der ILIT/SCIT Gruppe gesehen.

Schlussfolgerungen und klinische Bedeutung: Die Wirksamkeit des ILIT Protokolls war nach sechs Monaten mit einer LVM Monotherapie vergleichbar. Wenn die ILIT mit SCIT weitergeführt wurde, konnte eine günstige Antwort gesehen werden.

要約

背景: アレルゲン特異的免疫療法(ASIT)は、犬アトピー性皮膚炎(cAD)に対して有効な治療法である。また、リンパ内免疫療法(ILIT)は , 臨床効果発現までの時間を短縮する効果が期待される。

目的: 本研究の目的は、ILIT月6回注射とlokivetmab月3回注射を併用した場合の臨床効果をlokivetmab月1回注射と168日後に比較することであった。ILITで治療した犬を、さらに6ヶ月間の皮下免疫療法(SCIT)でモニターすること。

供試動物: cADを有するオーナー所有犬36頭。

材料と方法: この二重盲検無作為化試験において、犬はILITの月6回の注射と月3回のLVM注射の併用(ILIT群)または月6回のlokivetmab注射(LVM群)のいずれかを受けた。毎月、痒みのVisual Analog Scale(pVAS)、Canine Atopic Dermatitis Extent and Severity Index, 4th iteration(CADESI-04)、投薬スコア(MS)で評価した。また、QoL(Quality of Life)質問票も実施された。成功は、pVASが50%以上減少し、CADESI-04のスコアが10以下であることと定義された。168日以降、ILIT群は12ヶ月後の主観的評価までSCITを継続した

結果: 168日後の治療基準は、ILIT群11.1%、LVM群11.8%が達成した。両群とも平均pVASスコアおよびCADESIスコアの有意な低下が認められた(p < 0.001)。ILIT群はLVM群と比較してMSが高い傾向にあった。QOLはLVM群で良好であった(p = 0.01)。12ヶ月後、ILIT/SCIT群の77.8%の犬で主観的な良〜優の反応が見られた。
結論と臨床的関連性: このILITプロトコルの有効性は、6カ月時点でLVM単剤療法と同等であった。ILITをSCITで継続した場合、良好な反応が見られた。

摘要
背景: 过敏原特异性免疫疗法(ASIT)是治疗犬特应性皮炎(cAD)的有效方法。淋巴结内免疫疗法(ILIT)可能有助于缩短临床疗效。
目的: 比较6个月ILIT注射联合3个月洛基韦单抗(LVM)注射,与每月LVM单药治疗在第168天的临床疗效。监测接受ILIT治疗的犬额外六个月的皮下免疫疗法(SCIT)。
动物: 36只客户饲养的cAD患犬。
材料和方法: 在这项双盲随机研究中,犬接受了六个月的ILIT注射,并结合三个月的LVM注射(ILIT组)或六个月的LV注射(LVM组)。采用瘙痒视觉模拟量表(pVAS)、犬特应性皮炎程度和严重程度指数第4次迭代(CADESI-04)和药物评分(MS)进行每月评估。还进行了生活质量(QoL)问卷调查。成功率预先定义为pVAS降低≥50%,CADESI-04评分≤10。D168后,ILIT组继续进行SCIT,直到12个月时进行主观评估
结果: ILIT组11.1%和LVM组11.8%的患犬在D168达到了治疗基准。两组患者的平均pVAS和CADESI评分均显著下降(p<0.001)。与LVM相比,ILIT组有MS升高的趋势。LVM的生活质量更好(p=0.01)。在12个月时,ILIT/SCIT组77.8%的犬的主观性反应达到良好至极好。
结论和临床相关性: 此ILIT方案在6个月时的疗效与LVM单药治疗相当。当继续进行ILIT和SCIT时,可以看到有利的反应。

Resumo
Contexto: A imunoterapia alérgeno-específica (ASIT) é uma terapia eficaz para a dermatite atópica canina (cAD). A imunoterapia intralinfática (ILIT) é potencialmente benéfica na diminuição do tempo de eficácia clínica.
Objetivo: Comparar a eficácia clínica de seis injeções mensais de ILIT combinadas com três injeções mensais de lokivetmab (LVM) com LVM mensal em monoterapia no Dia (D)168. Monitorar cães tratados com ILIT por mais seis meses de imunoterapia subcutânea (SCIT).
Animais: Trinta e seis cães de clientes com DAC.
Materiais e Métodos: Neste estudo randomizado, duplo-cego, os cães receberam injeções mensais de ILIT durante seis meses combinadas com três injeções mensais de LVM (grupo ILIT) ou seis injeções mensais de LVM (grupo LVM). Foram realizadas avaliações mensais com Escala Visual Analógica de Prurido (pVAS), Índice de Extensão e Gravidade da Dermatite Atópica Canina, 4ª iteração (CADESI-04) e escores de medicação (MS). Um questionário de Qualidade de Vida (QoL) também foi administrado. O sucesso terapêutico foi definido como redução ≥50% em pVAS e CADESI-04 ≤10. Após D168, o grupo ILIT continuou com SCIT até avaliação subjetiva com 12 meses.
Resultados: O ideal de tratamento em D168 foi alcançado por 11,1% do grupo ILIT e 11,8% do grupo LVM. Uma diminuição significativa nos escores médios de pVAS e CADESI foi observada em ambos os grupos ($p < 0,001$). O grupo ILIT teve uma tendência para maior MS em comparação com LVM. A QoL foi melhor no LVM ($p = 0,01$). Aos 12 meses, foi observada uma resposta subjetiva boa a excelente em 77,8% dos cães no grupo ILIT/SCIT.
Conclusão e relevância clínica: A eficácia deste protocolo ILIT foi comparável à monoterapia LVM em seis meses. Quando ILIT foi continuado com SCIT, uma resposta favorável foi observada.