Received: 18 February 2022 | Accepted: 18 September 2022

DOI: 10.1111/vde.13138

Veterinary Dermatology

ORIGINAL ARTICLE

A randomised, double-blinded comparison between subcutaneous rush and intralymphatic allergen immunotherapy induction in atopic dogs

Ralf S. Mueller[1] | **Yuri Zablotski**[1] | **Katja Baumann**[1] | **Teresa Boehm**[1] | **Bettina Kasper**[1] | **Christoph Klinger**[2] | **Maarten Monke**[1] | **Laura Udraite-Vovk**[1] | **Tamara Weitzer**[1] | **Natalie K. Y. Gedon**[1]

[1]Centre for Clinical Veterinary Medicine, LMU Munich, Munich, Germany

[2]Tierklinik Stuttgart Plieningen, Stuttgart, Germany

Correspondence
Ralf S. Mueller, Centre for Clinical Veterinary Medicine, LMU Munich, Veterinaerstr. 13, 80539 Munich, Germany.
Email: r.mueller@lmu.de

Present address
Katja Baumann, Tierklinik Germering, Germering, Germany
Natalie K. Y. Gedon, North Carolina State University, Raleigh, North Carolina, USA
Laura Udraite-Vovk, Tierklinik Haar, Haar, Germany

Funding information
German Society of Cynological Research

Abstract

Background: Atopic dermatitis (AD) is one of the most common skin diseases in small animal practice. Allergen immunotherapy (AIT) is the only curative treatment for the disease, and oral, subcutaneous and intralymphatic administration of allergens are commonly employed.

Objectives: To compare the efficacy of AIT following an induction phase with intralymphatic injections (ILIT) or rush immunotherapy (RIT).

Animals: Fifty privately owned dogs with AD.

Materials and Methods: In a double-blinded study, dogs were randomly assigned to either four monthly ILIT of allergen extract or RIT with five injections administered subcutaneously at hourly intervals on the first day. They were assessed by validated scores; Canine Atopic Dermatitis Lesion Index (CADLI) and pruritus Visual Analog Scale (PVAS) at the beginning of the study and after 1, 3, 6 and 12 months. The latter were performed daily for 7 days before each revisit. Medication scores and a total clinical score were calculated and compared between each group and time point.

Results: There was no significant difference in CADLI and PVAS scores, or CADLI and medication scores between groups at any of the time points. A significant improvement with both ILIT and RIT was seen in total and pruritus scores, respectively. An owner global assessment of good-to-excellent treatment efficacy was seen in 40% of the dogs; total scores improved by 27% and 35% in the RIT and ILIT group, respectively. Adverse effects were not seen.

Conclusions and Clinical Relevance: Induction of AIT can be conducted either as RIT or ILIT with no loss in efficacy.

INTRODUCTION

Canine atopic dermatitis (cAD) is a common skin disease in small animal practice.[1,2] Although its pathogenesis is a topic of active research, the exact pathogenesis is not yet completely elucidated.[3–5] Canine atopic dermatitis is diagnosed by clinical history, physical examination and the exclusion of all differential diagnoses for each particular patient.[6] A number of effective therapies are available for management of cAD.[7,8] The only specific treatment, however, is allergen (–specific) immunotherapy (AIT), where offending allergens are classically injected subcutaneously to induce a regulatory response and a resulting improvement of clinical signs.[9,10] Initially, the amount of allergen extract injected is gradually increased over weeks to months (induction therapy), until a maintenance protocol is reached. In humans, there are a number of different ways to perform this induction. Classically weekly injections with increasing doses are administered until

the maintenance dose is reached and given every 4–8 weeks to cluster methods.[11] The amount injected and the injection intervals need to be adjusted to the individual patient to achieve maximal efficacy.[10,12] In rush immunotherapy (RIT) protocols, higher doses are administered at 15–60 min intervals over a 1–3 day period until the maintenance dose is achieved.[13] Accelerated immunotherapy build-up schedules aim at achieving the benefits of immunotherapy more quickly, as the maintenance dose is reached sooner. In addition, a reduced number of visits to the veterinarian saves the owner time, hopefully increasing compliance with and perceived convenience of this treatment. Rush and cluster immunotherapy schedules are the two most common accelerated schedules used in human medicine.[13] With a cluster immunotherapy schedule, the animal receives two to four allergen doses sequentially in a single day of treatment on nonconsecutive days, reaching the maintenance dose after 4–8 weeks. In RIT protocols, doses are administered every 30–60 min until the maintenance dose is achieved. Different rush protocols have been reported in the management of atopic dogs.[14–16] RIT also is described in two feline case studies, although a long-term therapeutic outcome has not been reported in that species.[17,18] Long-term, a good-to-excellent response to RIT was seen in 70% of the dogs in a retrospective study,[19] and total scores (reflecting the severity of cAD) decreased by >50% in 45% of the dogs in a prospective, double-blinded study.[16] Although the time to efficacy was shorter with RIT compared to conventional immunotherapy in one double-blinded, randomised trial, the difference between the two groups was not statistically significant, possibly due to the low number (10) of patients included in each group.[16]

More recently, other forms of immunotherapy such as oromucosal/sublingual immunotherapy and intralymphatic immunotherapy (ILIT) have been described.[20–24] Data on sublingual therapy are sparse,[20,22] and, based on a small pilot study, its efficacy is lower than that seen with ILIT and subcutaneous immunotherapy.[22] ILIT has been used in humans for more than a decade[25] and has been evaluated in dogs in several studies.[21–24] It is unknown, however, if induction of tolerance is facilitated by intralymphatic injections when compared to other protocols.

The aim of this study was to compare the outcome of AIT over a 12 month period in a larger number of dogs, using two different induction protocols (RIT and ILIT).

MATERIALS AND METHODS

Study design, objectives and ethics

In this prospective, randomised, double-blinded study, 50 privately owned dogs previously diagnosed with atopic dermatitis (AD) were included. Diagnosis of AD was by clinical examination, history and the ruling out of other possible causes of pruritus.[6] Owners signed a consent form before the inclusion of their dogs. The study was approved by the ethics committee of the Faculty of Veterinary Medicine/LMU Munich under the number 108-28-1-2018. Based on previous pilot data with atopic dogs undergoing immunotherapy, where the mean Canine Atopic Dermatitis Lesion Index (CADLI) score after treatment was 10 ±8 (standard deviation) and based on a power of 80% and a significance level of 0.05, 25 dogs in each group were necessary to identify a difference in outcome of 40%.

Randomisation and blinding

The participating dogs were randomly assigned to two groups with the help of a computer program website (Graphpad; https://www.graphpad.com/quickcalcs/randomize1.cfm, last accessed on 26.1.2018). Only the study coordinators responsible for filling the syringes [placebo (saline) or allergen extract] during the induction period knew which group each dog was assigned to. The injections were administered and the patients clinically evaluated by a blinded veterinary dermatological referral clinician or dermatology resident.

Study intervention

Allergens for individual allergen extract solutions were chosen based on correlation of the clinical history with results of intradermal testing (allergens obtained from Nextmune, Lelystad, Netherlands) or serum testing for allergen-specific immunoglobulin (Ig)E based on the recombinant Fc epsilon receptor test (Heska Laboratories) as described previously.[26] The Artuvetrin allergen extract consists of an individual mixture of alum-precipitated allergens (Nextmune). Between two and 12 allergens were included in the extract, with a median (and mean) of four allergens. The injections on Day (D) 0 were administered based on a rush protocol in the RIT group and intralymphatically in the ILIT group as shown in Table 1.

TABLE 1 Injection protocol on day 0 of allergen immunotherapy in dogs treated with intralymphatic injections (ILIT; group A) or rush immunotherapy (RIT, group B)

Time point	A	B
Hour 0	0.1 ml i.l. allergen extract, 0.2 ml s.c. placebo	0.1 ml i.l. placebo, 0.2 ml s.c. allergen extract
Hour 1	0.4 ml s.c. placebo	0.4 ml s.c. allergen extract
Hour 2	0.6 ml s.c. placebo	0.6 ml s.c. allergen extract
Hour 3	0.8 ml s.c. placebo	0.8 ml s.c. allergen extract
Hour 4	1.0 ml s.c. placebo	1.0 ml s.c. allergen extract

Abbreviations: i.l., intralymphatic; s.c, subcutaneous.

TABLE 2 Injection schedule of allergen extract in dogs treated with intralymphatic injections (ILIT; group A) or rush immunotherapy (RIT, group B) after day 0

Time point	Group A	Group B
Week 4	0.1 ml i.l. allergen extract, 1.0 ml s.c. placebo	0.1 ml i.l. placebo, 1.0 ml s.c. allergen extract
Week 8	0.1 ml i.l. allergen extract, 1.0 ml s.c. placebo	0.1 ml i.l. placebo, 1.0 ml s.c. allergen extract
Week 12	0.1 ml i.l. allergen extract, 1.0 ml s.c. placebo	0.1 ml i.l. placebo, 1.0 ml s.c. allergen extract
After week 12	1.0 ml s.c. allergen extract monthly or adjusted frequency and dose according to predetermined criteria	

Abbreviations: i.l., intralymphatic; s.c, subcutaneous.

The *Ln. popliteus* on alternating limbs was used for the first four appointments. Allergens were injected in the lymph node or subcutaneously, depending on the group, every 4 weeks for 3 months as outlined in Table 2. The ILIT group received 0.1 ml intralymphatic allergen solution and 1.0 ml subcutaneous saline solution, and the "regular" group received 0.1 ml intralymphatic saline solution and 1.0 ml subcutaneous allergen extract.

Starting at 4 months both groups received only subcutaneous injections of allergen extract in an identical fashion. If a short-term increase of pruritus in the days following the allergen injection occurred on two occasions, then the amount injected was reduced by 0.2 ml, while an increase of pruritus before the allergen injection on two occasions resulted in an interval of 3 weeks between injections; this was further adjusted on a patient-to-patient basis. The average volume injected at the end of the study was 0.8 ml (range 0.3–1 ml) administered on average every 3 weeks (range 1–7 weeks). Treatment of approximately 40% of the dogs resulted in an adjusted maintenance protocol.

Clinical assessment

Owners completed a questionnaire regarding their pet's history on the first visit. At the beginning of the study, they were asked to estimate the pruritus of their animals using a validated pruritus Visual Analog Scale (PVAS)[27,28] and clinicians determined the lesion severity using CADLI, a validated lesion score.[29] In addition, medication scores were determined using a scoring system published previously[19,30] and adapted to our study as shown in Table S3. Owners were asked to keep a log book of their dogs' daily pruritus scores and to contact the clinic for further advice if there were any changes before and after the subsequent injections of allergen extract. Any adverse reactions and concurrent treatments were recorded in the above-mentioned diary. After 1, 3, 6 and 12 months, dogs were re-evaluated. Daily pruritus scores were recorded for 30 days before the revisits at 1, 3, 6 and 12 months. The mean score of the last 7 days before the visit was used for statistical evaluation. Dose and frequency of the allergen extract injections were modified as needed as described above. An owner global assessment of treatment efficacy was also recorded, as excellent, good, fair, poor or no response.

Statistics

Primary outcome measures were an improvement in CADLI scores and the number of dogs achieving CADLI scores in the range of normal dogs or those with mild AD at study end (i.e. dogs with CADLI <8); an improvement in PVAS and the number of dogs with scores in the range of normal dogs or those with mild AD at study end (i.e. dogs with PVAS <3.6) and an improvement in medication and in total scores (see below). The mean pruritus scores of the previous 7 days and the previous 30 days before the visits were calculated for that visit and the Spearman correlation coefficient *r* between the two means and the pruritus score on the day of the visit was determined. CADLI, the mean PVAS scores of the last 7 days before the visit and medication scores were normalised (rescaled to the common range of values between 0 and 1) so that all three features contributed equally to the result. Then a total score was calculated by adding three normalised scores together, for example, for the time point of 0 days: total score 0 = CADLI 0 + PVAS 0 + Medscore 0. A linear mixed effects model was used to evaluate the scores and time points with different treatments. All data wrangling and statistical analyses were conducted using R Statistical language (v4.0.3; R Core Team, 2020). Packages used in the current study are listed in Table S1. Further details on the statistical methods are outlined in File S1. The secondary outcome measure was the percentage of dogs whose owner rated the overall response to treatment as "good" or "excellent".

RESULTS

Study objects

Fifty dogs were included in the study: 25 in the ILIT and 25 in the RIT group. However, one dog of the ILIT group was lost to follow-up because the owner moved during the study. Details of the signalment and history of these dogs can be found in Table S2. The mean age was 4.1 years (range 1.5–10 years), and the mean disease duration was 2.4 years (range 0.5–7.5 years).

Clinical assessment

There was no significant difference in CADLI and PVAS scores between groups at any of the time points. A

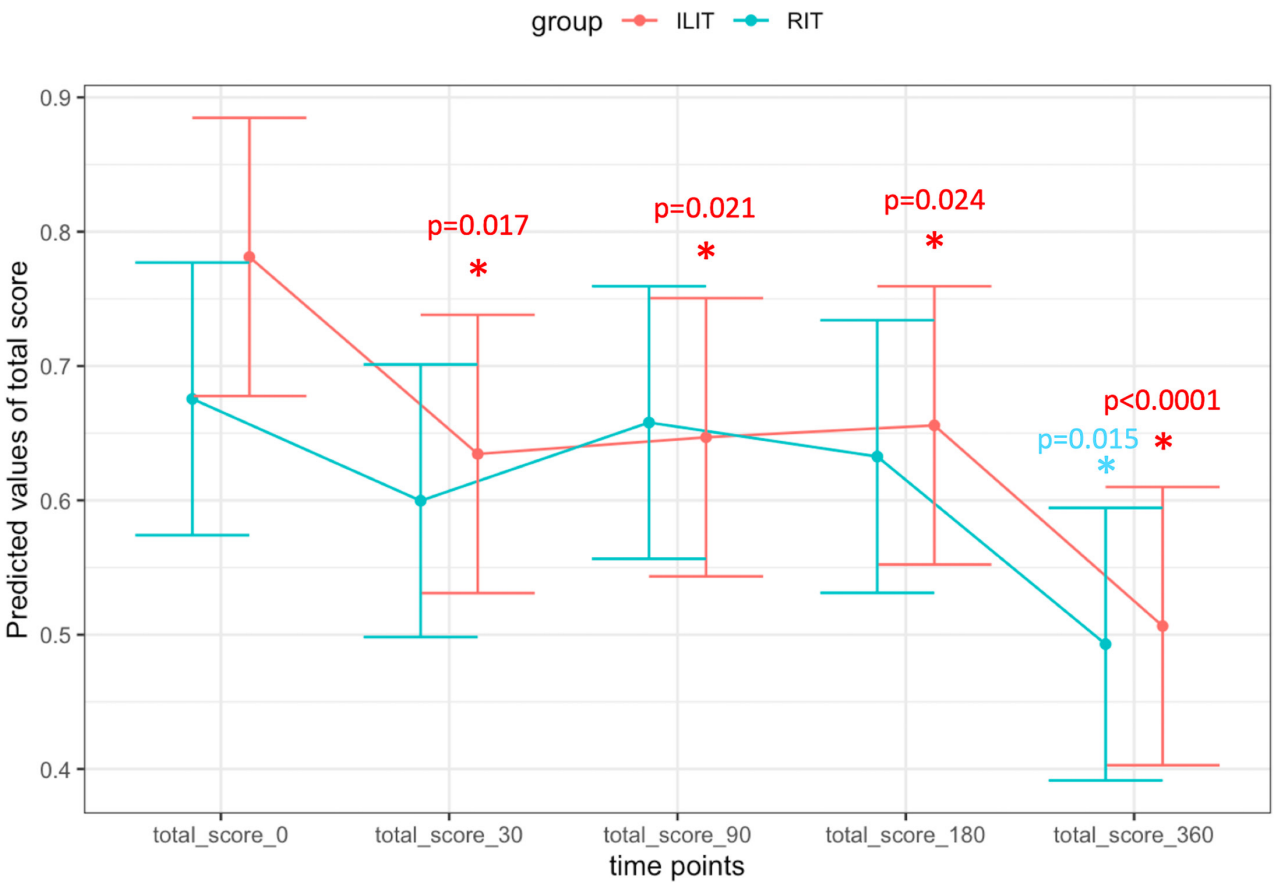

FIGURE 1 Total scores of dogs treated with intralymphatic injections (ILIT) and rush immunotherapy (RIT) before (total_score_0) and after 1 month (total_score_30), 3 months (total_score_90), 6 months (total_score_180) and 12 months (total_score_360). Significant differences to baseline (day 0) are marked with an asterisk and the corresponding *p*-value.

significant improvement with both ILIT and RIT was seen in total scores (Figure 1) and pruritus scores (Figure 2) over time, and there was no significant difference in CADLI or medication scores between time points in either group and no difference between the groups for these parameters. Raw data of PVAS and CADLI over the year are provided in Table S4.

Nine of 24 dogs receiving ILIT and six of 25 dogs receiving RIT had a pruritus score ≤3 indicating mild disease before therapy, and 16 of 24 and 16/25 (respectively) after 1 year of therapy; this was a significant improvement in the RIT group (Fisher's exact test, $p = 0.0096$) and not in the ILIT group (Fisher's exact test, $p = 0.77$). For a CADLI value ≤4, the corresponding numbers were 11 of 24 before and 11 of 24 after ILIT, and 13 of 25 before and 16 of 25 after RIT (Fisher's exact test, $p = 1.0$ and $p = 0.57$, respectively). Nine of 24 dogs (38%) receiving ILIT improved by ≥50% in CADLI value compared to 14 of 25 dogs (56%) receiving RIT; for PVAS, the corresponding values were 10 of 24 (42%) with ILIT and 14 of 25 (56%) with RIT. Those differences were not significant (Fisher's exact test, $p = 0.26$ and $p = 0.39$). The owner reported global assessment of treatment efficacy was good or excellent in 10 of 25 dogs in the RIT and 10 of 24 dogs in the ILIT group.

Mean pruritus scores in the last seven and 30 days before the visit correlated extremely well, with a Spearman coefficient $r = 0.997$ ($p < 0.0001$). By contrast, the correlation between the pruritus score of the visitation day and the mean score of the last 7 days was much lower ($r = 0.56$).

Adverse effects attributed to the immunotherapy were not seen in any of the dogs. One dog had seizures that were not temporally related to the injections. Seven dogs showed intermittent sneezing and four dogs intermittent epiphora, which were considered to be possible manifestations of atopic disease and again were not temporally related to the allergen extract injections. Diarrhoea was seen in five dogs – one bout during the year in four dogs, and intermittent in one dog, and also not associated with the allergen injection. One incidence of superficial bacterial pyoderma during the 12 month study was seen in three dogs each.

DISCUSSION

This study showed a significant improvement of pruritus and total scores of dogs treated with both types of AIT (RIT and ILIT), yet there was no statistical difference in outcome measures between intralymphatic and RIT in any of the measured parameters. Adverse effects related to immunotherapy were not seen in any of the dogs.

With RIT, the induction period is abbreviated, often from 4 weeks down to 1 day.[14–16] In human medicine, RIT provides earlier clinical improvement and improved convenience, although it is associated with a higher

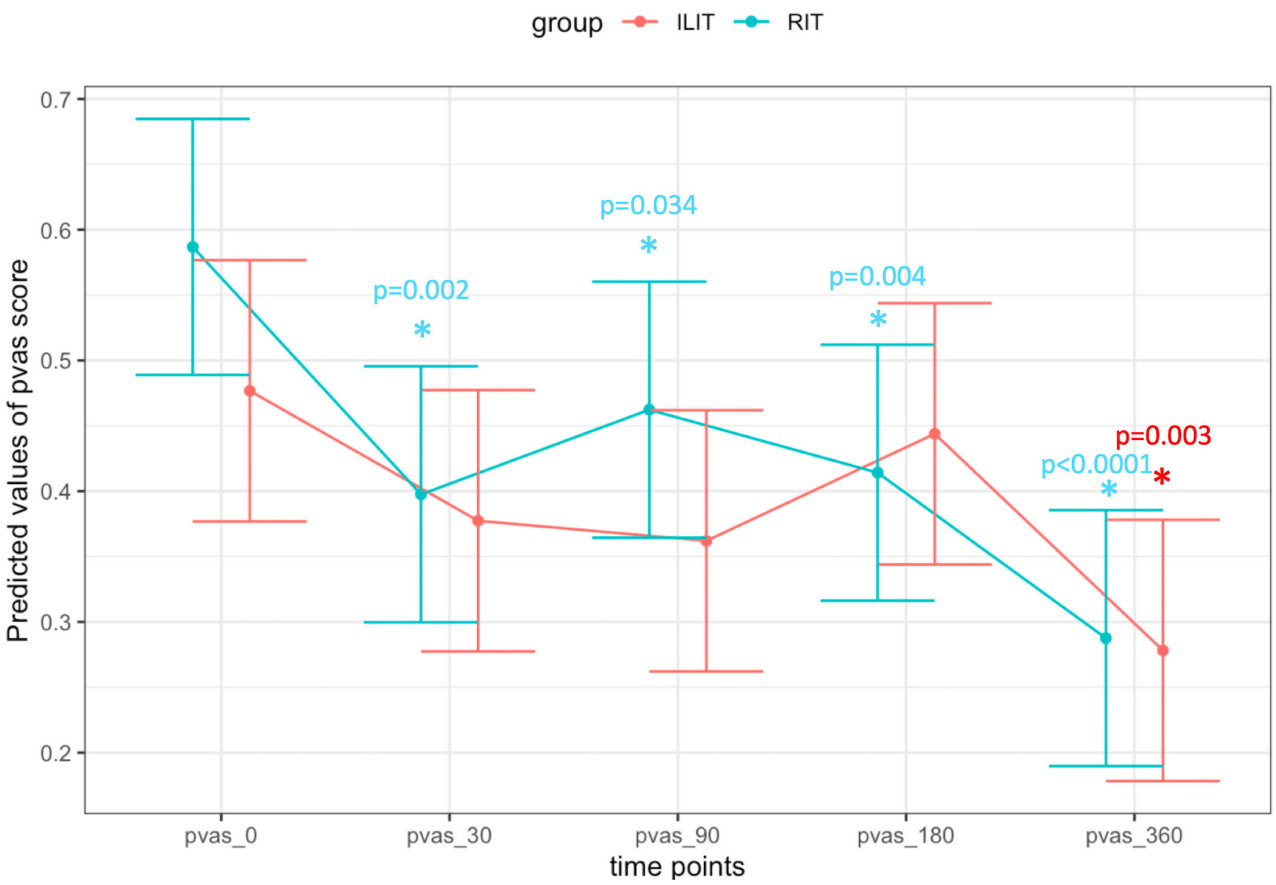

FIGURE 2 Total pruritus scores of dogs treated with intralymphatic injections (ILIT) and rush immunotherapy (RIT) before (pvas_0) and after 1 month (pvas_30), 3 months (pvas_90), 6 months (pvas_180) and 12 months (pvas_360). Significant differences from baseline (day 0) are marked with an asterisk and the corresponding *p*-value.

risk of systemic adverse events,[13] which is why RIT in humans is conducted in a hospital setting. RIT has been studied in the dog and its long-term efficacy has been comparable to published data for classic immunotherapy.[15,16,19] In one double-blinded, randomised comparison, RIT in the dog also was associated with a faster induction of tolerance compared to conventional immunotherapy, although the difference was not significant, possibly owing to the fact that were only 10 dogs in each study group.[16] With ILIT, a high allergen concentration is introduced directly into a lymph node, where presumably exposure to a large number of T cells is greatly facilitated. This theoretically should lead to an increased immune response. In humans, only three intralymphatic allergen injections were reported to alleviate clinical signs in patients allergic to Fel d 1[25] and in patients with pollen-induced rhinoconjuctivitis for up to 3 years,[31,32] and were associated with less adverse events than subcutaneous allergen injections.[32] ILIT has been evaluated in dogs in several studies.[21–24] However, data for prolonged efficacy have not been convincing. One study, in which patients received four to six monthly intralymphatic injections of allergen extract and were followed for 12 months, close to two thirds of the dogs subsequently needed additional allergen injections.[24] That study did not evaluate whether time to maximal response or success rate was different from previous reports of subcutaneous immunotherapy in dogs. The long-term effects of repeated intralymphatic injections of allergen extracts over years are unknown and adjuvant-associated allergens are of particular potential concern. However, ILIT was well-tolerated in dogs included in previous studies,[21–24] and four injections administered monthly were considered safe based on published data.

Allergen immunotherapy has been evaluated in many studies, although double-blinded, randomised trials over 12 months are rarely undertaken. In the only placebo-controlled study published evaluating canine AIT, 59% of dogs treated with ASIT and 21% of dogs treated with placebo improved by >50%, and nine of 27 dogs treated with ASIT and four of 16 dogs treated with placebo went into complete remission.[33] Incomplete data regarding inclusion criteria, data collection and lack of intention-to-treat analyses render the evaluation of these results difficult. In another double-blinded, randomised study, conventional and RIT were compared in dogs with AD and an improvement of >50% in pruritus scores was observed in 45% and 55% of the dogs, respectively.[16] Lesion scores improved likewise in both groups. A >50% improvement in approximately half of the patients was seen in most other studies evaluating AIT in the dog.[9] However, in many of the older studies, validated pruritus or lesion scores were not used even if, at that time, available.[34–36] When the improvements in CADLI and PVAS were calculated for dogs in this study, they corresponded approximately with these previously reported numbers.

There was no difference between ILIT and RIT at any time point with regard to pruritus scores or lesion

severity. In other published studies evaluating solely ILIT[21,24] or solely RIT,[16,19] results approximately correspond to our findings. One recently published study comparing ILIT with conventional subcutaneous and sublingual immunotherapy in atopic dogs[22] found improvement with both subcutaneous and intralymphatic administration of allergens in contrast to sublingual application. In a similar protocol, dogs received ILIT for 3 months and subsequently were switched to subcutaneous maintenance immunotherapy. In contrast to our study, ILIT in that study seemed to perform even better than subcutaneous immunotherapy, albeit that the number of dogs evaluated in each group was very small.[22] One of the aims of RIT is to achieve a faster improvement than conventional immunotherapy. It is unclear if ILIT also is characterised by a rapid response. In this study, both therapies did not differ in their scores after 3, 6 and 12 months, indicating that there is no difference in time to efficacy.

There was no significant improvement in CADLI scores with either treatment. Another randomised, double-blinded study evaluating conventional versus low dose immunotherapy (1.0 ml vs. 0.1 ml allergen extract as maintenance dose) in dogs with AD did not identify a difference between those two protocols, lesion scores decreased significantly in both groups in contrast to pruritus scores.[37] It should be noted that in that study, the lack of improvement in pruritus scores was possibly a consequence of the low scores at the beginning of the study (26 of 29 enrolled dogs had a pruritus score of ≤3). Likewise, the lack of a significant difference in lesion scores in our study may have resulted from the fact that half of the dogs had mild CADLI scores at inclusion in the study.

Pruritus in allergic dogs varies with the current allergen load and consequently can vary from day to day. This is illustrated in this study by the lower correlation coefficient of the pruritus scores on the visitation day compared to the mean scores of the last seven and 30 days respectively. Previous published studies of cAD have determined the pruritus score on the examination day, which may not always reflect the overall improvement of an atopic dog over time. It may even be possible that the stress associated with a clinic visit influences pruritus scores on the day. In this study, the mean scores of the last 7 and 30 days correlated extremely well and as such it is concluded that documentation of pruritus would be sufficient if a daily pruritus diary for the last 7 days before the visit is recorded and the mean of those 7 days is used as the basis against which to assess pruritus in atopic dogs.

It was recently recommended to report three outcome measures in trials evaluating dogs with AD: 1, the percentages of dogs with veterinarian-assessed skin lesions and 2, owner-rated pruritus manifestation scores in the range of normal dogs or those with mild AD; and 3, a good-to-excellent global assessment by the pet owners of their perception of treatment efficacy.[38] Total scores are used in the evaluation of human AD or atopic eczema. Lesion and pruritus scores are combined with psychological factors such as emotional impact or acceptability of treatment and sleep disturbances in the Recap of atopic eczema (RECAP) score[39,40] or the Atopic Dermatitis Control Tool (ADCT).[40,41] Psychological factors cannot be evaluated easily in dogs with AD, yet a validated lesion score[29] and pruritus score[27,28] were part of the total scores calculated in this study. The owner-reported global assessment of a good-to-excellent response was seen in 40% of the dogs, which approximates to previous published studies.

In this study, alum-precipitated allergens were used. Previous studies of allergen-specific immunotherapy in general used either alum-precipitated[19,33,42,43] or aqueous allergens[16,34,44] and achieved similar success rates. In previous studies, ILIT also used either alum-precipitated[22,24] or aqueous allergens.[23] An initial study did not follow the ILIT with subcutaneous allergen injections and dogs deteriorated quickly after initial improvement.[23] Later studies continued immunotherapy long-term with subcutaneous injections and had better results.[22,24] The results of our study are consistent with previous results.

One limitation of this study was that dogs were treated with other medications in addition to the AIT. As dogs with AD frequently develop allergic flares with deterioration in clinical signs, it was deemed unethical as well as simply difficult to achieve good owner compliance over the duration of 1 year without permitting treatment of such flares as appropriate. Consequently, a medication score used in previous studies[19,30] was modified as new drugs used in atopic dogs such as lokivetmab and oclacitinib had to be incorporated. To reflect the actual disease state at the time of the visit, medications used in the month before presentation were included in the score. These medication scores are not validated at this point in time. Medication scores for long-term trials in cAD were recently recommended for a more limited number of drugs,[45] yet this information was not available when our study was commenced.

The intralymphatic injections were administered in the popliteal lymph nodes by inserting the needle under palpation control. This was considered sufficient as the lymph nodes were readily palpable in all dogs. Ultrasonographic control of the intralymphatic injection was not considered necessary. However, in humans it was recently reported that clinical response seems to depend on successful ILIT injections and low-quality injections should be acknowledged as a possible reason for treatment failure in human patients treated with ILIT.[46] It is possible that not all injections were administered directly into the lymph node in these atopic dogs, a further limitation of this study.

In conclusion, intralymphatic and RIT both seem equally suited as induction protocols for AIT in dogs with AD with success rates comparable to previous publications.

AUTHOR CONTRIBUTIONS

Yury Zablotski: Data curation; formal analysis; investigation; methodology; software; validation; visualization; writing – review and editing. **Katja Baumann:** Data curation; investigation; project administration;

writing – review and editing. **Teresa MSA Boehm:** Conceptualization; investigation; project administration; writing – review and editing. **Bettina Kasper:** Data curation; investigation; project administration; writing – review and editing. **Christoph Klinger:** Conceptualization; investigation; writing – original draft. **Marten Mohnke:** Data curation; investigation; project administration; writing – review and editing. **Laura Udraite-Vovk:** Conceptualization; investigation; methodology; project administration; supervision; writing – review and editing. **Tamara Weitzer:** Data curation; investigation; project administration; writing – original draft. **Natalie KY Gedon:** Conceptualization; funding acquisition; investigation; methodology; project administration; writing – review and editing.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Amelie von Vogts-Rhetz and Viviane Kinnula for their help with the study, all the owners for participating in such a long-lasting study and Sonya Bettenay for proof-reading the manuscript. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

This research was funded by the German Society of Cynological Research.

CONFLICT OF INTEREST

Ralf Mueller has acted as a consultant or received support for studies or lectures from Artuvet, Bayer Animal Health, Ceva Animal Health, Ecuphar, Elanco Animal Health, Greer Laboratories, Heska Laboratories, Hill's, Royal Canin, MSD Animal Health, Nextmune, Synlab, Virbac Animal Health and Zoetis. Christoph Klinger acts as a consultant for and has received support for lectures from Neoplas GmbH.

ORCID

Ralf S. Mueller https://orcid.org/0000-0001-5835-5910
Katja Baumann https://orcid.org/0000-0001-7536-9628
Teresa Boehm https://orcid.org/0000-0001-7886-0017
Christoph Klinger https://orcid.org/0000-0003-1570-3078
Tamara Weitzer https://orcid.org/0000-0002-8068-2288
Natalie K. Y. Gedon https://orcid.org/0000-0003-0224-9144

REFERENCES

1. Klinger C, Krause A, Rösch B, Werhahn P, Weinrich V, Müller R. Kleintiermedizin in Deutschland: Analyse des Fallaufkommens. Praktischer Tierarzt. 2016;97:774–87.
2. Lund EM, Armstrong PJ, Kirk CA, Kolar LM, Klausner JS. Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. J Am Vet Med Assoc. 1999;214:1336–41.
3. Marsella R, Sousa CA, Gonzales AJ, Fadok VA. Current understanding of the pathophysiologic mechanisms of canine atopic dermatitis. J Am Vet Med Assoc. 2012;241:194–207.
4. Nuttall TJ, Marsella R, Rosenbaum MR, Gonzales AJ, Fadok VA. Update on pathogenesis, diagnosis, and treatment of atopic dermatitis in dogs. J Am Vet Med Assoc. 2019;254:1291–300.
5. Eichenfield LF, Stripling S, Fung S, Cha A, O'Brien A, Schachner LA. Recent developments and advances in atopic dermatitis: a focus on epidemiology, pathophysiology, and treatment in the pediatric setting. Paediatr Drugs. 2022;24:293–305.
6. DeBoer DJ, Hillier A. The ACVD task force on canine atopic dermatitis (XV): fundamental concepts in clinical diagnosis. Vet Immunol Immunopathol. 2001;81:271–6.
7. Olivry T, Bizikova P. A systematic review of randomized controlled trials for prevention or treatment of atopic dermatitis in dogs: 2008–2011 update. Vet Dermatol. 2013;24:97–117. e25-6.
8. Olivry T, DeBoer DJ, Favrot C, Jackson HA, Mueller RS, Nuttall T, et al. Treatment of canine atopic dermatitis: 2015 updated guidelines from the international committee on allergic diseases of animals (ICADA). BMC Vet Res. 2015;11:210.
9. Loewenstein C, Mueller RS. A review of allergen-specific immunotherapy in human and veterinary medicine. Vet Dermatol. 2009;20:84–98.
10. Mueller RS, Jensen-Jarolim E, Roth-Walter F, Marti E, Janda J, Seida AA, et al. Allergen immunotherapy in people, dogs, cats and horses – differences, similarities and research needs. Allergy. 2018;73:1989–99.
11. Jutel M, Kosowska A, Smolinska S. Allergen immunotherapy: past, present, and future. Allergy Asthma Immunol Res. 2016;8:191–7.
12. Griffin CE, Hillier A. The ACVD task force on canine atopic dermatitis (XXIV): allergen-specific immunotherapy. Vet Immunol Immunopathol. 2001;81:363–83.
13. Calabria CW. Accelerated immunotherapy schedules. Curr Allergy Asthma Rep. 2013;13:389–98.
14. Herrmann I, Loft KE, Olivry T. Shortened immunotherapy dose-escalation saves time, but is it safe? A case–control study comparing the rates of adverse reactions between conventional and fast-escalation subcutaneous immunotherapy protocols during the induction phase. Vet Dermatol. 2020;31:454-e120.
15. Mueller RS, Bettenay SV. Evaluation of the safety of an abbreviated course of injections of allergen extracts (rush immunotherapy) for the treatment of dogs with atopic dermatitis. Am J Vet Res. 2001;62:307–10.
16. Mueller RS, Fieseler KV, Zabel S, Rosychuk RAW. Conventional and rush immunotherapy in canine atopic dermatitis. In: Hillier A, Foster AP, Kwochka KW, editors. Advances in veterinary dermatology, volume 5. Oxford: Blackwell Publishing; 2005. p. 60–9.
17. Trimmer AM, Griffin CE, Boord MJ, Rosenkrantz WS. Rush allergen specific immunotherapy protocol in feline atopic dermatitis: a pilot study of four cats. Vet Dermatol. 2005;16:324–9.
18. Jones SM, Bloom P. Rush immunotherapy in two cats with atopic skin syndrome. J Fel Med Surg Open Rep. 2021;7:1–5.
19. Hobi S, Mueller RS. Efficacy and safety of rush immunotherapy with alum-precipitated allergens in canine atopic dermatitis. Tierarztl Prax Ausg K Kleintiere Heimtiere. 2014;42:167–73.
20. DeBoer DJ, Verbrugge M, Morris M. Clinical and immunological responses of dust mite sensitive, atopic dogs to treatment with sublingual immunotherapy (SLIT). Vet Dermatol. 2016;27:82–7. e23.
21. Fischer N, Rostaher A, Favrot C. Intralymphatic immunotherapy: an effective and safe alternative route for canine atopic dermatitis. Schweiz Arch Tierheilkd. 2016;158:646–52.
22. Fischer NM, Rostaher A, Favrot C. A comparative study of subcutaneous, intralymphatic and sublingual immunotherapy for the long-term control of dogs with nonseasonal atopic dermatitis. Vet Dermatol. 2020;31:365-e96.
23. Hatzmann K, Mueller RS. Practicability and safety of intralymphatic allergen-specific immunotherapy in dogs with atopic dermatitis. Annual congress of the European Society of Veterinary Dermatology, volume 22. Bruxelles, Belgium: Veterinary Dermatology; 2011. p. 463–4.
24. Timm K, Mueller RS, Nett-Mettler CS. Long term effects of intralymphatic immunotherapy (ILIT) in canine atopic dermatitis. Vet Dermatol. 2018;29:123-e49.

25. Senti G, Crameri R, Kuster D, Johansen P, Martinez-Gomez JM, Graf N, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. J Allergy Clin Immunol. 2012;129:1290–6.
26. Mallmann S, Klinger C, Classen J, Wagner I, Klima A, Castelletti N, et al. Clinical relevance of intradermal test results in atopic dogs. Tierarztl Prax Ausg K Kleintiere Heimtiere. 2021;49:349–56.
27. Hill PB, Lau P, Rybnicek J. Development of an owner-assessed scale to measure the severity of pruritus in dogs. Vet Dermatol. 2007;18:301–8.
28. Rybnicek J, Lau-Gillard PJ, Harvey R, Hill PB. Further validation of a pruritus severity scale for use in dogs. Vet Dermatol. 2009;20:115–22.
29. Plant JD, Gortel K, Kovalik M, Polissar NL, Neradilek MB. Development and validation of the canine atopic dermatitis lesion index, a scale for the rapid scoring of lesion severity in canine atopic dermatitis. Vet Dermatol. 2012;23:515-e103.
30. Mueller RS, Fieseler KV, Fettman MJ, Zabel S, Rosychuk RAW, Ogilvie GK, et al. Effect of omega-3 fatty acids on canine atopic dermatitis. J Small Anim Pract. 2004;45:293–7.
31. Hylander T, Larsson O, Petersson-Westin U, Eriksson M, Georén SK, Winqvist O, et al. Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. Respir Res. 2016;17:10.
32. Senti G, Prinz Vavricka BM, Erdmann I, Diaz MI, Markus R, McCormack SJ, et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. Proc Natl Acad Sci U S A. 2008;105:17908–12.
33. Willemse A, Van den Brom WE, Rijnberk A. Effect of hyposensitization on atopic dermatitis in dogs. J Am Vet Med Assoc. 1984;184:1277–80.
34. Mueller RS, Bettenay SV. Long-term immunotherapy of 146 dogs with atopic dermatitis – a retrospective study. Austral Vet Practitr. 1996;26:128–32.
35. Nuttall TJ, Thoday KL, van den Broek AH, Jackson HA, Sture GH, Halliwell RE. Retrospective survey of allergen immunotherapy in canine atopy. Vet Rec. 1998;143:139–42.
36. Scott KV, White SD, Rosychuk RAW. A retrospective study of hyposensitization in atopic dogs in a flea scarce environment. In: Ihrke PJ, Mason IS, White SD, editors. Advances in veterinary dermatology. Oxford, UK: Pergamon Press; 1993. p. 79–87.
37. Colombo S, Hill PB, Shaw DJ, Thoday KL. Effectiveness of low dose immunotherapy in the treatment of canine atopic dermatitis: a prospective, double-blinded, clinical study. Vet Dermatol. 2005;16:162–70.
38. Olivry T, Bensignor E, Favrot C, Griffin CE, Hill PB, Mueller RS, et al. Development of a core outcome set for therapeutic clinical trials enrolling dogs with atopic dermatitis (COSCAD'18). BMC Vet Res. 2018;14:238.
39. Howells LM, Chalmers JR, Gran S, Ahmed A, Apfelbacher C, Burton T, et al. Development and initial testing of a new instrument to measure the experience of eczema control in adults and children: recap of atopic eczema (RECAP). Br J Dermatol. 2020;183:524–36.
40. Thomas KS, Apfelbacher CA, Chalmers JR, Simpson E, Spuls PI, Gerbens LAA, et al. Recommended core outcome instruments for health-related quality of life, long-term control and itch intensity in atopic eczema trials: results of the HOME VII consensus meeting. Br J Dermatol. 2021;185:139–46.
41. Simpson E, Eckert L, Gadkari A, Mallya UG, Yang M, Nelson L, et al. Validation of the atopic dermatitis control tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis. BMC Dermatol. 2019;19:15.
42. Prost C. Treatment of feline asthma with allergen avoidance and specific immunotherapy: experience with 20 cats. Rev FranAllergol Immunol Clin. 2008;48:409–13.
43. Willemse T, Bardagi M, Carlotti DN, Ferrer L, Fondati A, Fontaine J, et al. Dermatophagoides farinae-specific immunotherapy in atopic dogs with hypersensitivity to multiple allergens: a randomised, double blind, placebo-controlled study. Vet J. 2009;180:337–42.
44. Keppel KE, Campbell KL, Zuckermann FA, Greeley EA, Schaeffer DJ, Husmann RJ. Quantitation of canine regulatory T cell populations, serum interleukin-10 and allergen-specific IgE concentrations in healthy control dogs and canine atopic dermatitis patients receiving allergen-specific immunotherapy. Vet Immunol Immunopathol. 2008;123:337–44.
45. Saridomichelakis MN, Favrot C, Jackson HA, Bensignor E, Prost C, Mueller RS. A proposed medication score for long-term trials of treatment of canine atopic dermatitis sensu lato. Vet Rec. 2021;188:e19.
46. Skaarup SH, Graumann O, Schmid J, Bjerrum A-S, Skjold T, Hoffmann HJ. The number of successful injections associates with improved clinical effect in intralymphatic immunotherapy. Allergy. 2021;76:1859–61.

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: Mueller RS, Zablotski Y, Baumann K, Boehm T, Kasper B, Klinger C, et al. A randomised, double-blinded comparison between subcutaneous rush and intralympathic allergen immunotherapy induction in atopic dogs. Vet Dermatol. 2023;34:91–98. https://doi.org/10.1111/vde.13138

Résumé

Contexte: La dermatite atopique (DA) est l'une des maladies de la peau les plus courantes chez les petits animaux. L'immunothérapie allergénique (AIT) est le seul traitement curatif de la maladie, et l'administration orale, sous-cutanée et intralymphatique d'allergènes est couramment utilisée.

Objectifs: Comparer l'efficacité de l'AIT après une phase d'induction avec des injections intralymphatiques (ILIT) ou une immunothérapie en rush (RIT).

Animaux: Cinquante chiens privés atteints de DA.

Matériels et méthodes: Dans une étude en double aveugle, des chiens ont été assignés au hasard à quatre ILIT mensuels d'extrait d'allergène ou à RIT avec cinq injections administrées par voie sous-cutanée à des intervalles d'une heure le premier jour. Ils ont été évalués par des scores validés ; Canine Atopic Dermatitis Lesion Index (CADLI) et Prurit Visual Analog Scale (PVAS) au début de l'étude et après un, trois, six et 12 mois. Ces dernières ont été effectuées quotidiennement pendant sept jours avant chaque visite de suivi. Les charges médicamenteuses et un score clinique total ont été calculés et comparés entre chaque groupe et chaque point dans le temps.

Résultats: Il n'y avait aucune différence significative dans les scores CADLI et PVAS, ou les scores CADLI et les médicaments entre les groupes à aucun moment. Une amélioration significative avec ILIT et RIT a été observée

dans les scores totaux et de prurit, respectivement. Une évaluation globale par le propriétaire de l'efficacité du traitement allant de bonne à excellente a été observée chez 40 % des chiens ; les scores totaux se sont améliorés de 27 % et 35 % dans les groupes RIT et ILIT, respectivement. Aucun effet indésirable n'a été observé.
Conclusions et pertinence clinique: L'induction de l'AIT peut être réalisée soit en RIT soit en ILIT sans perte d'efficacité.

Resumen
Introducción: La dermatitis atópica (AD) es una de las enfermedades de la piel más comunes en la práctica de pequeños animales. La inmunoterapia con alérgenos (AIT) es el único tratamiento curativo para la enfermedad, y comúnmente se emplea la administración oral, subcutánea e intralinfática de alérgenos.
Objetivos: Comparar la eficacia de AIT después de una fase de inducción con inyecciones intralinfáticas (ILIT) o inmunoterapia rápida (RIT).
Animales: Cincuenta perros de propietarios particulares con AD
Materiales y métodos: En un estudio doble ciego, los perros fueron asignados aleatoriamente a ILIT de extracto de alérgeno o RIT con cinco inyecciones administradas por vía subcutánea a intervalos de una hora el primer día. Fueron evaluados mediante puntuaciones validadas; Índice de Lesión de Dermatitis Atópica Canina (CADLI) y Escala Visual Análoga de Prurito (PVAS) al inicio del estudio y después de uno, tres, seis y 12 meses. Estos últimos se realizaron diariamente durante siete días antes de cada revisita. Se calcularon y compararon las puntuaciones de medicación y una puntuación clínica total entre cada grupo y punto de tiempo.
Resultados: No hubo diferencias significativas en las puntuaciones de CADLI y PVAS, ni en las puntuaciones de CADLI y de medicación entre los grupos en ninguno de los puntos temporales. Se observó una mejora significativa tanto con ILIT como con RIT en las puntuaciones totales y de prurito, respectivamente. Se observó una evaluación global del propietario de la eficacia del tratamiento de buena a excelente en el 40 % de los perros; las puntuaciones totales mejoraron en un 27 % y un 35 % en el grupo RIT e ILIT, respectivamente. No se observaron efectos adversos.
Conclusiones y relevancia clínica: La inducción de AIT se puede realizar como RIT o ILIT sin pérdida de eficacia.

Zusammenfassung
Hintergrund: Die atopische Dermatitis (AD) ist die häufigste Hauterkrankung in der Kleintierpraxis. Die Allergen Immuntherapie (AIT) ist die einzig heilende Behandlung dieser Erkrankung, wobei häufig eine orale, subkutane und intralymphatische Verabreichung der Allergene angewendet wird.
Ziele: Der Vergleich der Wirksamkeit von AIT nach einer Induktionsphase mit intralymphatischen Injektionen (ILIT) oder einer Rush Immuntherapie (RIT).
Tiere: Fünfzig Hunde in Privatbesitz mit AD.
Materialien und Methoden: In einer doppelblinden Studie wurden Hunde zufällig eingeteilt, um entweder alle vier Monate ILIT eines Allergenextrakts oder RIT mit fünf Injektionen am ersten Tag, die stündlich subkutan verabreicht wurden, zu erhalten. Sie wurden mit validierten Methoden beurteilt; dazu wurde der Canine Atopic Dermatitis Lesion Index (CADLI) und die Pruritus Visual Analog Scale (PVAS) am Beginn der Studie, sowie nach einem, drei, sechs und 12 Monaten eingesetzt. Letztere wurde vor jedem neuerlichen Besuch täglich sieben Tage lang angewendet. Es wurde die Medikation und eine totale klinische Bewertung kalkuliert und zwischen den einzelnen Gruppen und Zeitpunkten verglichen.
Ergebnisse: Es bestand zwischen den Gruppen zu keinem der Zeitpunkte ein signifikanter Unterschied bei CADLI und PVAS-Bewertungen, oder zwischen CADLI und Medikationen. Eine signifikante Verbesserung sowohl mit ILIT als auch mit RIT konnte anhand der Gesamtverbesserung bzw der verbesserten Juckreizwerte gesehen werden. Eine Gesamtbewertung der BesitzerInnen ergab bei 40% der Hunde eine gut-bis-exzellente Wirksamkeit der Behandlung; die Gesamtwerte verbesserten sich um 27% bzw 35% in der RIT bzw ILIT Gruppe. Es wurden keine Nebenwirkungen gesehen.
Schlussfolgerungen und klinische Bedeutung: Die Einführung der AIT kann ohne einen Wirksamkeitsverlust sowohl mit RIT wie auch mit ILIT gestartet werden.

要約
背景:　アトピー性皮膚炎(AD)は、小動物診療において最も一般的な皮膚疾患の一つである。アレルゲン免疫療法(AIT)は本疾患の唯一の根治療法であり、アレルゲンの経口、皮下、リンパ内投与が一般的である。
目的: 本研究の目的は、　導入期を経たAITの効果を、リンパ内注射(ILIT)またはラッシュ免疫療法(RIT)と比較することであった。
対象動物: ADを有するオーナー所有犬50頭
材料と方法: 月4回のアレルゲン抽出物によるILIT、または初日に1時間間隔で5回皮下投与するRITに犬を無作為に割り付け、二重盲検試験を実施した。犬アトピー性皮膚炎病変指数(CADLI)および痒みのVisual Analog Scale(PVAS)を、試験開始時および1、3、6、12ヵ月後に評価した。PVASは、各再診の7日前から毎日実施した。投薬スコアおよび臨床的な総スコアを算出し、各群間および各時点で比較した。
結果:　CADLIおよびPVASスコア、CADLIおよび薬物療法スコアは、いずれの時点でも群間で有意差はなかった。ILIT、RITの両方で、総スコア、PVASスコアにそれぞれ有意な改善がみられた。オーナーグローバル評価では、40%

の犬で治療効果が良~優と評価され、総スコアはRIT群、ILIT群でそれぞれ27%、35%改善した。また、有害事象は認められなかった。
結論と臨床的意義: AITの導入はRITでもILITでも有効性を損なうことなく実施できる。

摘要
背景: 特应性皮炎 (AD) 是小动物临床中最常见的皮肤病之一。过敏原免疫治疗 (AIT) 是该病唯一的根治方法，通常采用过敏原口服、皮下和淋巴结内给药。
目的: 比较淋巴内注射 (ILIT) 或快速免疫治疗 (RIT) 诱导期后 AIT 的疗效。
动物: 50只私人拥有的 AD 犬。
材料和方法: 在一项双盲研究中，犬被随机分配到4个月 ILIT 过敏原提取物或 RIT 组，第1天皮下注射5次，每小时一次。在研究开始时以及1、3、6和12个月后，通过经验证的评分进行评估；犬特应性皮炎病变指数 (CADLI) 和瘙痒视觉模拟量表 (PVAS)。后者在每次复诊前每天进行，持续7天。计算并比较各组和时间点的用药评分和临床总评分。
结果: 在所有时间点，组间 CADLI 和 PVAS 评分、CADLI和药物治疗评分均无显著差异。ILIT 和 RIT 分别观察到总评分和瘙痒评分显著改善。在40%的犬中观察到良好-极佳治疗有效性的犬主人整体评估；RIT和 ILIT 组的总分分别改善了27%和35%。未见不良反应。
结论和临床相关性: 可以进行RIT 或 ILIT作为AIT的诱导，不会降低有效性。

Resumo
Contexto: A dermatite atópica (DA) é uma das dermatopatias mais comuns na clínica de pequenos animais. A imunoterapia alergênica (AIT) é o único tratamento curativo para a doença, e a administração subcutânea, oral e intralinfática de alérgenos são comumente empregadas.
Objetivos: Comparar a eficácia da AIT após fase de indução com injeções intralinfáticas (ILIT) ou imunoterapia em rush (RIT).
Animais: Cinquenta cães de proprietários com DA.
Materiais e métodos: Em um estudo duplo-cego, os cães foram aleatoriamente designados para ILIT mensal de quatro extratos de alergênicos ou RIT com cinco injeções administradas por via subcutânea em intervalos de uma hora no primeiro dia. Eles foram avaliados por escores validados; Canine Atopic Dermatitis Lesion Index (CADLI) e prurido Visual Analog Scale (PVAS) no início do estudo e após um, três, seis e 12 meses. Estes últimos foram realizados diariamente durante sete dias antes de cada revisita. Escores de medicação e um escore clínico total foram calculados e comparados entre cada grupo e ponto de tempo.
Resultados: Não houve diferença significativa nos escores CADLI e PVAS, ou CADLI e escores de medicação entre os grupos em nenhum dos momentos. Uma melhora significativa com ILIT e RIT foi observada nos escores total e de prurido, respectivamente. Uma avaliação global do proprietário da eficácia do tratamento de bom a excelente foi observada em 40% dos cães; os escores totais melhoraram em 27% e 35% no grupo RIT e ILIT, respectivamente. Efeitos adversos não foram observados.
Conclusões e relevância clínica: A indução de AIT pode ser realizada como RIT ou ILIT sem perda de eficácia.