

Long-term effects of intralymphatic immunotherapy (ILIT) on canine atopic dermatitis

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Background – Subcutaneous allergen immunotherapy (SCIT) is an established and efficacious therapy for canine atopic dermatitis (AD). In humans, intralymphatic immunotherapy (ILIT) was reported to be associated with fewer and less severe adverse effects than subcutaneous allergen immunotherapy and to be efficacious for several years after three intralymphatic injections.

Objective – To evaluate safety and effects of ILIT in a case series of dogs with (AD).

Animals – Fifty one privately owned dogs with AD.

Methods – Dogs received injections of 0.2 mL alum-precipitated allergen extract into the popliteal lymph nodes at monthly intervals for 3–5 months. Lesion scores, pruritus and medication scores were determined before and at three and 12 months after beginning immunotherapy, and compared in a per protocol analysis (PP) and an intention-to-treat analysis (ITT).

Results – Twenty two dogs completed the study and 29 dogs did not fulfil study completion criteria due to lack of a final study visit (21 of 29) or due to insufficient improvement (14 of 29). All scores improved during the study with both analyses. For pruritus and Quality of Life scores this improvement was significant with both analyses; for Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03 values and medication scores only with PP. The only rare adverse effects observed included mild swelling of the lymph node post-injection and increased pruritus.

Conclusion and clinical relevance – ILIT is safe and feasible, and provides long-lasting relief in some atopic dogs with a limited number of injections.

Introduction

Canine atopic dermatitis (AD) is a frequent skin disease in small animal practice,^{1,2} which is characterized by pruritus and lesions associated with self-trauma.³ Most frequently, extremities, face, ears and ventrum are affected.^{3,4} Secondary infections are commonly seen.⁵ Systematic reviews of treatment options for canine AD⁶ as well as treatment guidelines for practice^{7,8} have been published. Various symptomatic therapies to reduce pruritus are recommended for affected dogs, but the only specific therapy is allergen-specific immunotherapy (ASIT).^{6,7,9} With ASIT, an extract containing the offending allergens identified by history and intradermal testing or serum testing for allergen-specific IgE is injected

subcutaneously (subcutaneous immunotherapy, SCIT) or administered orally (sublingual immunotherapy, SLIT). The exact protocol varies depending on the patient and allergen source.¹⁰ Rush immunotherapy protocols have been evaluated for safety and efficacy.^{11,12} Evidence has been presented that ASIT increases peripheral tolerance by increasing T regulatory cells and IL-10 production.¹³

More recently, intralymphatic immunotherapy (ILIT) has been reported as a successful treatment for AD in mice.¹⁴ It also has been used safely and successfully in humans with allergic rhinitis due to pollens^{15–17} and cat allergens.^{18,19} Three monthly intralymphatic injections decreased nasal allergic symptoms and specific serum IgE, and caused fewer adverse events than subcutaneous immunotherapy. The improvement was long-lasting and similar to that seen in standard ASIT after three years.^{15–17}

Two studies have investigated the use of ILIT in dogs. One unpublished study compared ILIT with aqueous allergens with SCIT;²⁰ similar improvement was seen during the first three months, but clinical signs recurred in all dogs receiving ILIT within weeks of the last injection (R. Mueller, personal communication). A published study evaluated ILIT with alum-precipitated allergens in 20 dogs with AD with a follow-up time of six months.²¹

The aim of this study was to evaluate ILIT in a group of atopic dogs with a longer follow-up time than previous studies. It was hypothesized that ILIT with alum-precipitated allergens induces a better response rate and a more rapid response to therapy than other types of

Abbreviations: AD, atopic dermatitis; ASIT, allergen-specific immunotherapy; CADESI, Canine Atopic Dermatitis Extent and Severity Index; ILIT, intralymphatic immunotherapy; ITT, intention-to-treat analysis; PP, per protocol analysis; PVAS, pruritus Visual Analog Scale; QoL, Quality of Life scores; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy. Accepted 23 November 2017

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immunotherapy, and that it may result in longer-lasting remission of clinical signs of canine AD.

Material and Methods

Study dogs

Dogs with AD due to environmental allergens based on history, clinical signs and ruling out differential diagnoses were included in the study after owners were educated about the study and its possible risks and benefits, and consented to inclusion. All dogs fulfilled published criteria.²² Furthermore, all dogs with nonseasonal clinical signs underwent an elimination food trial over at least eight weeks prior to study inclusion. All dogs had elevated serum concentrations of allergen-specific IgE and/or positive intradermal test reactions.

Exclusion criteria included any prior treatment with ASIT, parasitic infestation or uncontrolled bacterial or yeast infection. Other concomitant antipruritic medications were acceptable (including antihistamines, steroids, ciclosporin and oclacitinib) if such medication had been given for at least four weeks at unchanged doses prior to inclusion into the study. Atopic dogs with concurrent adverse food reaction were included so long as the diet was not changed at least four weeks prior to inclusion and during the study.

Intervention

Allergens for ILIT (Greer®; Lenoir, NC, USA) were chosen based on the dog's history and results of intradermal testing or serum testing for allergen-specific IgE. The allergens were administered at 10% of the maintenance dose [0.1 mL of 20,000 PNU) for pollen and mould allergens and 0.1 mL of 1:100 w/v for mite allergens, respectively, adsorbed to 0.1 mL aluminium hydroxide]. Intralymphatic injections were administered at monthly intervals into one of the popliteal lymph nodes (alternating sides with each subsequent injection) under ultrasound guidance over three to five months. Needles of 25G × 5/8 inch and 1 mL syringes were used for injections. The number of intralymphatic injections (four to six) was chosen based on the clinical improvement of the individual dog. Sedation for the procedure was not required for any dog.

Clinical evaluation

Dogs were evaluated before immunotherapy and one, two, three, six and 12 months after study onset, although the one, two and six month visits were not evaluated statistically. In dogs with seasonal AD, the statistically evaluated visits were all scheduled within the dog's allergy season. Lesions of AD were scored using a validated lesion score, Canine Atopic Dermatitis Extent and Severity Index, third iteration (CADESI-03),^{23,24} from 0 to 5 in 62 body sites and the total score was determined by the sum of individual scores. Pruritus was scored with a validated Visual Analog Scale (VAS) from 0 to 10 with descriptions of various degrees of pruritus next to the score line.^{25,26} Medications were scored with a modified version of a medication score reported previously;^{27,28} details are shown in Table S1. Individual medication scores were calculated by the sum of assigned points. The owners filled out a questionnaire with 13 questions regarding the quality of life before the study, and three and twelve months after study onset.²⁹ A positive answer was rated 1 point, a negative answer was rated 0 points. The owners also gave a subjective overall assessment of the clinical response of their dog to ILIT. This was classified into different categories: clinical remission, marked improvement, slight improvement, no change and deterioration.

Withdrawal criteria

Dogs were removed from the study if they showed adverse reactions or signs of anaphylactic shock after allergen injection. Similarly, they were withdrawn if clinical signs deteriorated profoundly.

Statistical analyses

CADESI, pruritus, medication and Quality of Life (QoL) scores before the study and after three and 12 months were compared with a repeated measures ANOVA or (in case of data not normally distributed) a Friedman test and Dunn's multiple

comparisons test. A *P*-value ≤0.05 was considered significant. A per protocol (PP) analysis for all dogs completing the study and an intention-to-treat analysis (ITT) with the last value carried forward additionally evaluating dogs excluded from the study were both conducted. Because dogs with poor response to ILIT treatment after 4–6 injections were changed to subcutaneous ASIT, the PP analysis was biased toward the good responders to ILIT, and thus the ITT analysis was also performed.

Results

Fifty one dogs with AD were included in the study. Eight of these showed seasonal signs. Thirty four dogs were male of which 21 dogs were intact. Seventeen dogs were female of which 11 dogs were intact. Thirty two dog breeds were represented. The breeds most commonly affected were Labrador retrievers (*n* = 7), mongrels (*n* = 4) and German shepherd dogs (*n* = 3). The English bulldog, French bulldog, Jack Russell terrier, Parson Russell terrier, West Highland white terrier, Airedale terrier, Dalmatian and golden retriever were represented twice, and twenty one further breeds only once. The average age was 4.2 years (range 1–10 years).

Twenty two of those dogs completed the protocol with an average of 4.5 intralymphatic injections (15 dogs = 4 injections, 2 dogs = 5 injections and 5 dogs = 6 injections). They did not receive any further immunotherapy for the following six to eight months. The number of intralymphatic injections did not influence the outcome. Those dogs were included in the PP analysis. Twenty nine dogs were excluded from the PP analysis because they did not meet at least one criterion. Twenty one of those 29 dogs had missed the control visit at 12 months despite several attempts to contact owners. Six dogs did not improve sufficiently and received more than the allowed six intralymphatic injections. Five dogs were started on subcutaneous and two dogs on sublingual immunotherapy either directly after the completion of the intralymphatic injections due to insufficient response, or at a later point during the 12 month study period when signs recurred. Five of these seven dogs responded well to maintenance immunotherapy. Finally, one dog was withdrawn because of insufficient improvement during the first three months and one dog was withdrawn due to unrelated health problems.

Intralymphatic injections were well tolerated without sedation and only rare and minor adverse effects were recorded. These included mild enlargement of the lymph node and mildly increased pruritus for a few days after injection in three and two dogs, respectively.

Clinical evaluation

Mean lesional values, pruritus, medication and QoL scores at days 0, 90 and 360 are listed in Table 1. Pruritus scores, CADESI and medication scores are depicted in Figures 1, 2 and 3, respectively. Supporting Information Table S2 provides all study data of the 51 dogs included in this study.

Dogs in the PP and ITT analysis showed a significant improvement in CADESI-03 values between Day 0 and Day 90 and between Day 0 and Day 360 (Table 1). Pruritus scores improved significantly with both analyses between Day 0 and Day 360 and between Day 0 and Day 90

Table 1. CADESI, pruritus, medication and Quality of Life scores of dogs with atopic dermatitis before, after three and 12 months of allergen immunotherapy (mean $\pm$ standard deviation).

	Day 0	Day 90	Day 360
CADESI (PP)	29 $\pm$ 34	10 $\pm$ 14**	5 $\pm$ 6***
CADESI (ITT)	32 $\pm$ 39	15 $\pm$ 17**	12 $\pm$ 14****
PVAS (PP)	4.7 $\pm$ 2.3	3.0 $\pm$ 2.2*	1.9 $\pm$ 1.8****
PVAS (ITT)	5 $\pm$ 2.5	3.4 $\pm$ 2.5**	2.9 $\pm$ 2.3****
Medications (PP)	20 $\pm$ 20	20 $\pm$ 17	11 $\pm$ 13
Medications (ITT)	20 $\pm$ 18	17 $\pm$ 17	14 $\pm$ 15*
QoL (PP)	10.2 $\pm$ 2.3	12.2 $\pm$ 2.2*	12.8 $\pm$ 1.5*
QoL (ITT)	8.6 $\pm$ 2.4	10.3 $\pm$ 3.1*	10.0 $\pm$ 3.0***

PP per protocol analysis, ITT intention-to-treat analysis, CADESI Canine Atopic Dermatitis Extent and Severity Index, PVAS pruritus Visual Analog Scale, QoL Quality of Life scores.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

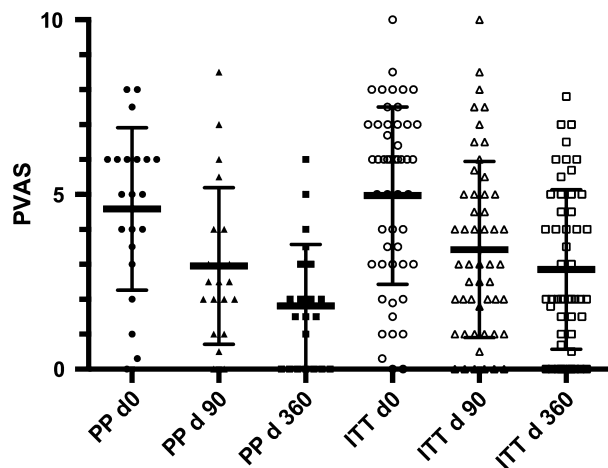


Figure 1. Scatter plot of pruritus scores of atopic dogs treated with intralymphatic immunotherapy as determined with a pruritus Visual Analog Scale (pVAS)(mean $\pm$ standard deviation).

PP, Per protocol analysis; ITT, intention to treat analysis; d0, day zero; d90, day 90; d360, day 360.

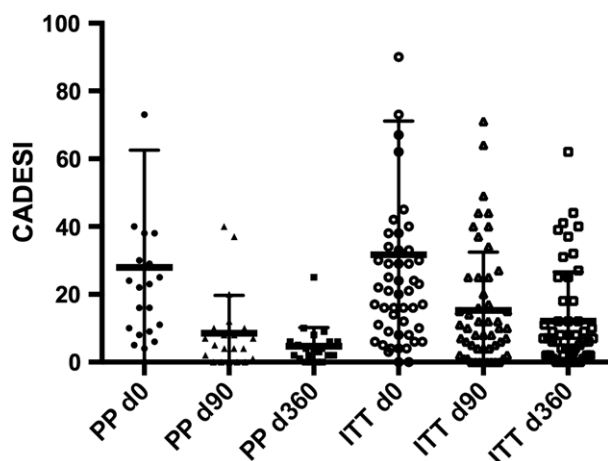


Figure 2. Scatter plot of Canine Atopic Dermatitis Extent and Severity Index (CADESI) scores of atopic dogs treated with intralymphatic immunotherapy (mean $\pm$ standard deviation).

PP, Per protocol analysis; ITT, intention to treat analysis; d0, day zero; d90, day 90; d360, day 360.

(Table 1). Although medication scores decreased between time points with both analyses, this difference was only significant in the ITT analysis between Day 0 and Day 360.

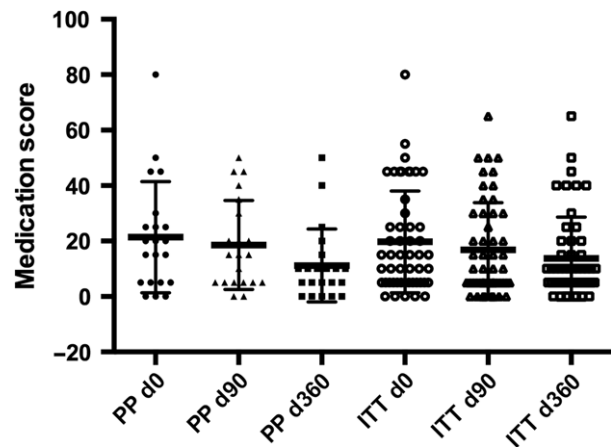


Figure 3. Scatter plot of the medication scores of atopic dogs treated with intralymphatic immunotherapy (mean $\pm$ standard deviation). PP, Per protocol analysis; ITT, intention to treat analysis; d0, day zero; d90, day 90; d360, day 360.

Ten of 51 dogs (19.61%) in the ITT analysis and six of 22 (27.27%) in the PP analysis showed at least 50% reduction of CADESI-03 and pruritus scores between Day 0 and Day 30; this was associated with reduced or unchanged medication scores. Fifteen of 51 dogs (29.41%) in the ITT analysis and eight of 22 dogs (36.36%) in the PP analysis demonstrated an improvement of $\geq 50\%$ in CADESI-03 and pruritus scores with reduced or unchanged medication scores from Day 0 to Day 90. For 22 of 51 dogs (43.12%) in the ITT analysis and 12 of 22 dogs (54.54%) in the PP analysis, improved $\geq 50\%$ from Day 0 to Day 360.

The QoL scores increased significantly in both analyses for both time points. The numbers of animals showing normal scores for lesions and pruritus as well as those showing only signs of mild AD increased with treatment, and the number of moderately and severely affected animals decreased (Table 2).

The overall assessment of clinical response to ILIT, subjectively graded by the dog owners on Day 0 and Day 360, showed that, in the ITT analysis, 30 of the 45 dogs (66.66%), for which the information was available, and in the PP analysis 19 of the 22 dogs (86.36%) responded to ILIT. Complete remission and marked improvement was seen in 18 of 45 dogs (40%) in the ITT analysis, and in 15 of 22 dogs (68.18%) in the PP analysis, respectively. In the ITT analysis 14 of 45 dogs and in the PP analysis four of 22 dogs were slight responders. Owners reported no improvement in 14 of 45 dogs (31%) and three of 22 dogs (14%), with ITT and PP analyses, respectively. Deterioration was not seen in the PP analysis and seen in only one dog in the ITT analysis.

Of the dogs with complete remission and marked clinical improvement, 16 of 18 dogs (88.88%) in the ITT analysis and 14 of 15 dogs (93.33%) in the PP analysis required no medication at all or no systemic therapy except for essential fatty acids on Day 360.

Discussion

This study demonstrates the safety and practicability of intralymphatic ASIT in dogs with canine AD and provides

Table 2. Number and percentage of atopic dogs in the different severity categories before and after 12 months of intralymphatic immunotherapy.

Severity category	CADESI Day 0	CADESI Day 360	PVAS Day 0	PVAS Day 360
Normal level (CADESI 0–9, pruritus 0.0–1.9)	PP six of 22 (27%) ITT 13 of 51 (25%)	PP 19 of 22 (86%) ITT 33 of 51 (64%)	PP three of 22 (14%) ITT eight of 51 (16%)	PP 11 of 22 (50%) ITT 18 of 51 (35%)
Mild AD (CADESI 10–34, pruritus 2.0–3.5)	PP 11 of 22 (50%) ITT 26 of 51 (51%)	PP three of 22 (14%) ITT 12 of 51 (24%)	PP three of 22 (14%) ITT nine of 51 (18%)	PP eight of 22 (36%) ITT 13 of 51 (25%)
Moderate AD (CADESI 35–59, pruritus 3.6–5.5)	PP three of 22 (14%) ITT five of 51 (10%)	PP 0 of 22 (0%) ITT five of 51 (10%)	PP six of 22 (27%) ITT seven of 51 (14%)	PP two of 22 (9%) ITT 12 of 51 (24%)
Severe AD (CADESI 60–180, pruritus 5.6–10.0)	PP two of 22 (9%) ITT seven of 51 (14%)	PP 0 of 22 (0%) ITT one of 51 (2%)	PP 10 of 22 (45%) ITT 27 of 51 (53%)	PP one of 22 (5%) ITT eight of 51 (16%)

AD atopic dermatitis, CADESI Canine Atopic Dermatitis Extent and Severity Index, ITT intention-to-treat analysis, PP per protocol analysis, PVAS pruritus Visual Analog Scale.

clinical evidence for successful management of this disease with intralymphatic allergen injections.

Three injections of ILIT led to long-lasting tolerance in a study of 58 humans with allergic rhinitis.¹⁵ Similar long-lasting effects were seen in some of the dogs in this study after four to six injections. Unfortunately, a large number of dogs had to be excluded from the PP analysis because they missed the last visit. This is a common problem with studies on allergen immunotherapy due to the extended duration of such trials. In the first placebo-controlled study about ASIT in atopic dogs, published more than three decades ago, the same number of dogs was initially included and a similar number completed the study, compared with our study.³⁰ Numerous dogs did not improve during ILIT or worsened after cessation of ILIT and immunotherapy was changed to subcutaneous administration. This indicates that a set number of intralymphatic allergen injections cannot replace ongoing long-term subcutaneous injections in all atopic dogs; although some dogs will respond satisfactorily, others will not.

Forty percent of dogs in the ITT analysis and 68% in the PP analysis showed at least marked improvement due to ILIT, as classified subjectively by the owners. This response rate corresponds to the efficacy of 60% described in a previous study on ILIT in dogs, and to that reported in several studies about SCIT and SLIT in dogs.^{10,21,30,31} Complete remission was seen in 13% of dogs in the ITT analysis and 24% in the PP analysis. Five dogs (four dogs from the PP, one dog from the ITT analysis) were followed up for four years and required no further systemic medication except for one to three intralymphatic injections per year to remain in remission. Thus, in some dogs, ILIT with alum-precipitated allergens can result in long-lasting clinical remission with a limited number of injections compared to SCIT and SLIT, where maintenance therapy is usually continued long-term. The use of aqueous allergens in another study investigating ILIT in dogs also led to a quick clinical remission but in contrast to the present study signs of AD recurred within weeks after the last injection.²⁰ Therefore, the use of alum-precipitated allergens seems to be important to induce a long-lasting effect of ILIT.

A $\geq 50\%$ reduction of CADESI-03 and pruritus scores was observed in one fifth of the dogs one month after the first intralymphatic injection. Medication scores were reduced or at least unchanged during this period. A comparable clinical response to ILIT was described in 20 dogs.²¹ These findings illustrate the potential of ILIT to induce a rapid clinical response.

Nine of 12 dogs (75%) with good clinical response to ILIT required no systemic medication on Day 180 in one study.²¹ Our numbers were even higher in both analyses ITT: [(16 of 18 dogs (89%), PP: 14 of 15 dogs (93%)], with most dogs requiring either no medication or just topical therapies and/or essential fatty acids on Day 360. A continuous decrease in pruritus and lesion scores with time was associated with the reduced need for medication.

Adverse effects with conventional allergen immunotherapy in dogs are rarely described. A common adverse effect is increased pruritus after allergen injection.¹⁰ Local swelling at the injection site also is seen. The most severe adverse effect, anaphylactic shock, occurs only very rarely in the dog.¹⁰ Mild adverse effects were occasionally seen with ILIT, which is in concordance with findings in human medicine, where intralymphatic injections were tolerated even better than subcutaneous injections.¹⁵ However, the number of patients in human and veterinary medicine undergoing ILIT is still small and long-term effects of repeated intralymphatic alum-precipitated allergen immunotherapy are not known in humans or animals.

There are several limitations of this study. Most importantly, the lack of a control group and of blinding increases bias of owners and clinicians. The number of dogs recruited, a validated pruritus and lesion score, as well as the medication scores, were attempts to minimize that bias. Secondly, a fair number of dogs were lost to follow-up and it is not known if those owners chose to discontinue collaboration because the dogs did clinically well (decreasing the motivation to continue to invest time and effort) or if there was an unsatisfactory response and owners chose to seek advice elsewhere. Loss to follow-up tends to be a problem with studies of long duration. Owner compliance may have been improved with financial compensation; however, this was not possible in this self-funded study. Nevertheless, although the PP analysis was biased for patients responding to therapy, the ITT analysis with the last value carried forward for the most part had similar results, and thus supported our findings. Finally, there was no clear protocol for adjunctive antipruritic therapy. Dogs were treated with a variety of medications based on the individual patient's response, and the owner's preferences and finances. Using a medication score was an attempt to permit evaluation of ILIT success in dogs receiving one or more concurrent drugs. Medication scores decreased during the study and thus it seems unlikely that the significant improvement seen was due to increased antipruritic medication.

Further studies, preferably prospective randomized blinded trials with clear protocols for adjunctive medical therapy, are needed to confirm our results, in order: to evaluate the long-term effects of repeated ILIT; to identify the ideal number and frequency of injections; and, possibly, to identify patient clinical features or biomarkers that help predict which dog may respond better to ILIT and which patient should receive SCIT. Double-blinded, randomized trials are needed to compare this treatment option with subcutaneous allergen injections. In addition, longer lasting studies than the 12 months recorded in this study are needed to determine the average time before recurrence of clinical signs.

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Supporting Information

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

Table S1. Point values assigned to different medications to determine medication scores of dogs

Table S2. Study data of 51 dogs undergoing intralymphatic immunotherapy.

Résumé

Contexte – L'immunothérapie spécifique d'allergène sous-cutanée (SCIT) est un traitement efficace et bien établi de la dermatite atopique canine (AD). Chez l'homme l'immunothérapie intra-lymphatique (ILIT) a été rapportée comme étant associée à moins d'effet secondaire que l'immunothérapie par voie sous-cutanée et efficace pendant plusieurs années après trois injections intra-lymphatiques.

Objectifs – Évaluer l'innocuité et les effets de l'ILIT pour une série de chiens atopiques.

Sujets – Cinquante et un chiens atopiques de propriétaires.

Méthodes – Les chiens recevant des injections de 0.2 mL d'extrait allergénique dans les nœuds lymphatiques poplités une fois par mois pendant 3-5 mois. Le score lésionnel, le prurit et les scores médicamenteux ont été déterminés avant et après trois et 12 mois d'immunothérapie et comparé par analyse PP (per protocole) et une analyse ITT (intention-to-treat).

Résultats – Vingt deux chiens ont complété l'étude et 29 chiens ne remplissaient pas les critères de fin d'en raison d'un manque de visite finale (21 sur 29) ou à une amélioration insuffisante (14 sur 29). Tous les scores se sont améliorés pendant l'étude pour les deux analyses. Pour le prurit et la qualité de vie, cette amélioration était significative pour les deux analyses; pour le CADESI-03 (Canine Atopic Dermatitis Extent and Severity Index) et les scores médicamenteux, seulement avec PP. Les seuls rares effets secondaires observés comprenaient un gonflement modéré du nœud lymphatique après l'injection et une augmentation du prurit.

Conclusion et importance clinique – L'ILIT est sûr, faisable et permet une amélioration de longue durée pour certains chiens atopiques avec un nombre limité d'injections.

Resumen

Introducción – la inmunoterapia subcutánea frente a alérgenos (SCIT) es una terapia establecida y eficaz para la dermatitis atópica canina (AD). En seres humanos, la inmunoterapia intralinfática (ILIT) se ha descrito como tratamiento que presenta menos efectos adversos que la inmunoterapia con alérgenos subcutáneos y que ha demostrado su eficacia durante varios años después de tres inyecciones intralinfáticas.

Objetivo – evaluar la seguridad y los efectos de ILIT en una serie de casos de perros con (AD).

Animales – cincuenta y un perros de propietarios privados con AD.

Métodos – los perros recibieron inyecciones de 0,2 ml de extracto de alérgeno precipitado con alumbre en los ganglios linfáticos poplíteos a intervalos mensuales durante 3-5 meses. Las evaluaciones de lesiones, el prurito y medicación se determinaron antes y a los tres y 12 meses después de comenzar la inmunoterapia, y se compararon en un análisis por protocolo (PP) y un análisis con intención de tratar (intention-to-treat analysis, ITT).

Resultados – veintidós perros completaron el estudio y 29 perros no cumplieron los criterios de finalización del estudio por la falta de una visita final (21 de 29) o debido a una mejoría insuficiente (14 de 29). Todas las valoraciones mejoraron durante el estudio con ambos análisis. Para las valoraciones de prurito y calidad de vida, esta mejora fue significativa con ambos análisis; para los valores del Índice de Extensión y Severidad de la Dermatitis Atópica Canina (CADESI)-03 y valores de medicación solo con el análisis PP. Los únicos efectos adversos observados incluyeron una leve hinchazón del ganglio linfático después de la inyección y un aumento del prurito.

Conclusión y relevancia clínica – ILIT es un método de tratamiento seguro y factible, y proporciona un alivio duradero en algunos perros atópicos con un número limitado de inyecciones.

Zusammenfassung

Hintergrund – Die subkutane Allergen Immuntherapie (SCIT) ist eine etablierte und wirksame Therapie bei der atopischen Dermatitis (AD) des Hundes. Beim Menschen wurde beschrieben, dass die intralymphatische Immuntherapie (ILIT) mit weniger Nebenwirkungen als die subkutane Allergen Immuntherapie auftrat und nach drei intralymphatischen Injektionen für einige Jahre wirksam war.

Ziel – Die Evaluierung der Sicherheit und der Wirksamkeit von ILIT in einer Fallserie von Hunden mit AD.

Tiere – Einundfünfzig Hunde mit AD in Privatbesitz.

Methoden – Die Hunde erhielten 3-5 Monate lang monatliche Injektionen von 0,2mL mit Aluminiumhydroxid präzipitierten Allergenextrakten in die Popliteallymphknoten. Die Bewertung der Veränderungen, der Juckreiz und die Werte der Medikamentenverabreichung wurden vor und drei und 12 Monate nach Beginn der Immuntherapie bestimmt und mittels Protokollanalyse (PP) und einer Intention-to-treat Analyse (ITT) verglichen.

Ergebnisse – Zweiundzwanzig Hunde beendeten die Studie. Neunundzwanzig Hunde erfüllten die Kriterien zur Beendigung der Studie nicht, da sie nicht zur Abschlussvisite (21 von 29) kamen oder nur eine unzureichenden Verbesserung (14 von 29) zeigten. Beiden Analysen zufolge verbesserten sich alle Werte während der Studie. Für den Juckreiz und die Lebensqualität war diese Verbesserung mittels beider Analysen signifikant; für die Werte des Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03 und für

die Werte der Medikamentenverabreichung allerdings nur mittels PP. Die nur selten beobachteten Nebenwirkungen bestanden in leichter Schwellung der Lymphknoten nach der Injektion und einem verstärkten Juckreiz.

Schlussfolgerung und klinische Bedeutung – ILIT ist eine sichere und machbare Behandlung, die eine langfristige Verbesserung bei einigen atopischen Hunden bringt, wobei nur eine limitierte Anzahl an Injektionen nötig ist.

要約

背景 – 皮下アレルギー免疫療法(SCIT)は、犬アトピー性皮膚炎(AD)の確立された有効な治療法である。人では、リンパ節内免疫療法(ILIT)が、皮下アレルギー免疫療法よりも有害事象が少なく、3回のリンパ節内注射後の数年間は有効であると報告されている。

目的 – ADに罹患した犬に対するILITの安全性および効果を評価すること。

供与動物 – ADに罹患した51頭の飼い犬。

方法 – 患犬は、ミョウバン沈殿抗原抽出物0.2mLを膝窩リンパ節内に毎月3～5ヶ月間注射された。病変スコア、掻痒および投薬スコアは、免疫療法開始前、および治療開始3ヵ月後と12ヵ月後に評価し、パープロトコル解析(PP)および包括解析(ITT)を実施した。

結果 – 22頭が治験を完遂し、29頭は治験最終日の来院がなかったため(29頭中21頭)あるいは十分な改善が認められなかったため(14頭中29頭)に、治験完遂基準を満たさなかった。両方の解析において、すべてのスコアが治験中に改善した。掻痒および生活の質スコアに関して、両方の解析で有意な改善が認められた。犬アトピー性皮膚炎の範囲および重症度指数(CADESI)-03スコアおよび投薬スコアはPPのみで有意差が認められた。観察された有害事象は、注射後のリンパ節の軽度な腫脹および掻痒の増加のみであった。

結論および臨床的な重要性 – ILITは安全で実行可能な治療法であり、限られた注射回数のみで長期間の改善を示したアトピー犬も認められた。

摘要

背景 – 皮下過敏原免疫療法(SCIT)是针对犬异位性皮炎(AD)建立的有效方案。据报道,在人类医学上,淋巴内免疫疗法(ILIT)与皮下过敏原免疫疗法相比副作用更小,并且在三次淋巴内注射后几年内都有效果。

目的 – 评估ILIT在(AD)一系列犬病例中的安全性和效果。

动物 – 五十一只私家异位性皮炎患犬。

方法 – 每月一次,将 0.2ml明矾沉淀过敏原提取物,注射到犬腘淋巴结,持续3-5个月。在开始免疫疗法之前和之后的三个月和十二个月时给病变、瘙痒和药物评分,并且比较每个方案分析(PP)和治疗意向分析(ITT)。

结果 – 二十二只犬完成了研究,29只犬没有达到实验标准而没有完成,其原因有的没有最终回访(21/29),有的没有明显好转(14/29)。在这两项分析研究过程中,所有分数均有提高。在两项分析中,瘙痒和生活质量评分都有明显改善;仅在PP中有犬异位性皮炎程度和严重性指数(CADESI)-03评分和药物评分。可观察到的唯一罕见副作用,包括注射后淋巴结轻度肿胀和瘙痒增加。

结论和临床意义 – ILIT是安全而可行的方案,并且注射次数有限,对有些异位性皮炎患犬能起到长效缓解的作用。

Resumo

Contexto – A imunoterapia alérgeno-específica subcutânea (SCIT) é uma terapia eficaz e estabelecida para a dermatite atópica canina (DA). Em humanos, a imunoterapia intralinfática (ILIT) foi associada a menos efeitos adversos que a imunoterapia alérgeno-específica subcutânea e sua eficácia tem sido relatada por muitos anos após três injeções intralinfáticas.

Objetivo – Avaliar a segurança e os efeitos de ILIT em uma série de casos de cães com DA.

Animais – Cinquenta e um cães com DA de proprietários.

Métodos – Os cães receberam injeções de 0,2 mL de extratos alergênicos em precipitado de alumínio no linfonodo poplíteo em intervalos mensais por três a cinco meses. Escores de lesões, prurido e medicação foram determinados antes e em três e 12 meses após o início da imunoterapia, e comparados em uma análise por protocolo (PP) e uma análise de intenção de tratar (ITT).

Resultados – Vinte e dois cães completaram o estudo e 29 cães não preencheram os critérios de conclusão do estudo devido a ausência da visita final (21 de 29) ou devido à melhora insuficiente (14 de 29). Todos os escores melhoraram durante o estudo em ambas as análises. Para os escores de prurido e qualidade de vida, a melhora foi significativa em ambas as análises; para os valores de Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03 e para os escores de medicação, apenas com o PP. O único efeitos adversos raros observados incluíram edema discreto do linfonodo após injeção e aumento de prurido.

Conclusão e relevância clínica – A ILIT foi segura e factível e proporcionou alívio duradouro em alguns cães atópicos com um número limitado de injeções.

Supporting Information

Table S1 Point values assigned to different medications to determine medication scores of dogs

Treatment	Points
No medication	0
Topical without steroids	5
Topical with steroids	10 (once daily) 5 (EOD or less)
EFAs	5
Antihistamines	10
Antibiotics, antifungals	20
Prednisolone <0.2 mg/kg/d	20
Prednisolone 0.2-0.5 mg/kg/d	30
Prednisolone 0.6-1 mg/kg/d	40
Prednisolone >1 mg/kg/d	50
Ciclosporin $\leq$ 1.25 mg/kg/d	20
Ciclosporin 2.5 mg/kg/d	30
Ciclosporin 5 mg/kg/d	40
Oclacitinib 0.4-0.6 mg/kg/d	40

Table S2: Study data of 51 dogs undergoing intralymphatic immunotherapy

Dog #	CADESI d 0	CADESI d 90	CADESI d 360	PVAS d 0	PVAS d 90	PVAS d 360	Med d 0	Med d 90	Med d 360	QoL d 0	QoL d 90	QoL d 360
1*	21	34	41	6	6.5	7	5	0	10	11		
2*#	24	0	0	3	2	2	15	15	15	9	10	10
3	11	0	0	2	1	0	0	0	0	10		12
4	73	0	20	7.5	4	6	5	45	5	8	11	10
5*+	12	14	12	7	2	7.8	5	35	25	10	12	10
6	16	7	3	6	5.5	2	20	15	10	8	11	
7*	8	27	27	6	6.5	6.5	5	5	5	9	8	8
8*	42	25	8	5	8	2	10	5	10	11	10	12
9	8	2	2	4	2.5	0	25	5	5	9	11	12
10*	17	16	4	3	3	0	10	0	0	2	8	12
11#	4	5	32	0	0	1	45	0	40	8	10	10
12*	29	1	1	6.7	1.8	1.8	5	5	5	10	12	12
13*	6	0	0	1.9	0	0	10	0	0	10	12	12
14*	62	25	25	7	5.7	5.7	5	10	10	2		
15*+	33	2	2	6.4	4	4	5	5	5	8	11	11
16	9	5	4	5	0	1.5	25	0	0	10	11	10
17*	6	17	6	8	7.5	7	15	30	20	6	5	5
18*	20	15	8	6	10	2	10	5	5	7	7	9
19*+	4	15	11	3	5	4	25	50	45	8	11	
20*+	217	25	37	10	0	4	45	30	30	4		
21	33	44	44	7	4.5	4.5	0	50	5	7		
22	23	4	10	6	2.5	3.5	15	15	15	11	11	10
23\$	3	0	0	6	5	5	45	65	65	9	4	4
24+	90	12	7	7.5	1	0	55	20	20	6		
25*	0	1	12	1	0	2	0	0	5	8	12	11
26*	30	10	9	3	1	0.7	15	5	10	10	10	11
27	38	8	9	0.3	0	1	15	5	5	12	12	12
28*+	17	49	18	8	4	4	10	10	5	9	9	
29	30	12	6	6	6	3	25	45	20	3	5	
30#+	16	6	7	2	1	0.5	45	5	40	9	11	
31\$	109	12	12	7	5	5	5	10	10	5		

32	22	1	6	6	3	2	45	20	10	7	9	12
33*	21	11	7	7	4	2	5	5	5	10	12	
34	16	8	6	4	2	3	15	15	10	11	11	8
35#	34	64	31	8.5	4	5.5	35	30	10	8	11	8
36	4	0	4	4	1	2	20	20	0	9	10	12
37	5	0	1	6	2	0	5	5	5	9	12	12
38	40	40	2	3.5	7	0	30	30	50	4	6	12
39	160	20	4	5	2	2	5	20	5	7		10
40	38	7	5	3	3	0	0	5	0	10		11
41	10	4	0	5	3	0	5	40	25	11	11	11
42	29	4	0	0	2.5	0	0	5	10	9	11	12
43	0	10	25	1	2	5	80	35	40	9	11	
44	6	10	2	8	4	1.5	45	10	0	10	11	12
45#	16	8	18	1	5	5	45	40	40	9	11	10
46*	67	44	62	7	3	6	20	25	15	8	10	
47	25	37	8	8	8.5	4	20	50	10	7	8	10
48	24	0	0	6	0.5	1.5	50	5	10	9	12	12
49*	14	40	40	3.5	4.5	4.5	45	5	5	5	5	5
50#	29	6	0	1.5	1	2	5	0	0	9	12	12
51*	45	71	39	8	7.5	6	10	5	5	5	7	

* = ITT, missing control visit on day 360, # = ITT, more than 6 ILITs, + = ITT, SCIT started, \$ = ITT, withdrawal,

CADESI = Canine Atopic Dermatitis Extent and Severity Index, ITT, Intention to Treat, PVAS = Pruritus Visual Analog Scale, Med = Medication score, QoL = Quality of Life score