

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

Ina Herrmann* , Klaus E. Loft† and Thierry Olivry* 

*Department of Clinical Sciences, College of Veterinary Medicine, NC State University, 1060 William Moore Drive, Raleigh, NC 27607, USA

†MSPCA Angell Memorial Hospital, 350 South Huntington Avenue, Boston, MA 02130, USA

Correspondence: Thierry Olivry, Department of Clinical Sciences, North Carolina State University, College of Veterinary Medicine, 1060 William Moore Drive, Raleigh, NC 27607, USA. E-mail: tolivry@ncsu.edu

Background – Allergen immunotherapy (AIT) is the only intervention believed to change the course of atopic diseases. As dogs appear to have fewer severe adverse events (AEs) compared to people receiving AIT, a prolonged dose-escalation induction phase might not be needed.

Objectives – To report the incidence and characteristics of AEs induced by a fast-escalation subcutaneous immunotherapy (f-SCIT) protocol compared to a conventional (c-SCIT) regimen.

Animals – One hundred dogs treated with either f-SCIT (Centre 1, 50 dogs) or c-SCIT (Centre 2, 50 dogs).

Methods and materials – A case-control study retrospectively evaluating AEs during the induction of AIT. We determined the incidence and type of AEs in each SCIT group; we also assessed factors such as self-limitation and the need for AE-associated protocol changes.

Results – Twelve of 100 dogs (12%) developed a SCIT-attributable AE during the induction phase, with one dog having a local and 11 having systemic reactions (nine Grade I, two Grade II, none of grades III or IV). Dogs treated with the f-SCIT had a significantly higher rate of AEs (11 of 50; 22%) compared to those receiving the c-SCIT (one of 50; 2%). Most of the AEs (10 of 11; 91%) in the f-SCIT group were mild and self-limiting.

Conclusions and clinical importance – The induction phase of f-SCIT is simpler, and the maintenance phase is reached faster than that of the c-SCIT. Despite its higher rate of AEs than with the c-SCIT regimen, the majority of f-SCIT-associated AEs were mild and self-limiting. Whether or not this f-SCIT protocol leads to a faster time-to-efficacy needs to be determined.

Introduction

Allergen immunotherapy (AIT) is currently the only specific therapy of allergic diseases believed to modify and change their course.^{1,2} Immunotherapy has been reported as beneficial in over two-thirds of treated dogs with atopic dermatitis (AD).^{3–12} In atopic dogs, as in humans, conventional AIT protocols consist of a slow and progressive dose-escalation (i.e. an “induction” period) before reaching the maintenance phase. This slow dose-escalation, which derives from the standard practice of subcutaneous immunotherapy (SCIT) in humans, has the primary objective of reducing the risk of development of severe acute adverse events (AEs) that have the potential to be fatal.¹³

In humans, systemic AEs resulting from SCIT are rare: they are reported in 2–5% of people with a fatality rate of

approximately 1:2–2.5 million injections.^{13–16} In the veterinary literature, AEs have been reported in 2–73% of dogs receiving SCIT, and the AE development rate has varied between protocols and administration methods.^{4,9,17–20} However, most reported AEs resulting from conventional SCIT in dogs have been reported as temporary, mild-to-moderate in nature and responsive to a decrease in the SCIT volume.^{4,9,17,18,20} Interestingly, in two placebo-controlled studies, the rate of AEs was similar between dogs receiving placebo [seven of 39 (18%)] or the active SCIT [38 of 414 (9%)].^{17,18}

As a result of the mild nature of the post-immunotherapy AEs reported in atopic dogs, one should – at least in theory – be able to inject dogs with the high maintenance doses of AIT more rapidly. Indeed, one retrospective study reported only one local reaction in 185 dogs receiving monthly injections of calcium phosphate-adsorbed SCIT after skipping the induction phase; unfortunately, there were only a few details on the influence of concurrent medications and a control group was not available.²¹ Theoretically, a shorter time to reach the maintenance AIT dose might lead to a faster onset of treatment

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benefit. Hypothesizing that a fast dose-escalation SCIT (f-SCIT) would have similar AE rates and severity grades compared to a conventional (c-SCIT) regimen, we modified our SCIT protocol to reduce the duration of the induction phase. Herein we report the results of a case-control study comparing the rate and types of AEs in f- versus c-SCIT protocols in dogs with AD.

Methods and materials

Study design

This study was a retrospective, two-centre, case-control study. The medical records of two specialized dermatology centres (Raleigh, NC and Boston, MA, USA) were searched for dogs with AD treated with SCIT with allergens purchased from the same company [ALK-Abello (ALK); Round Rock, TX, USA) in the same period (January 2017 to April 2019).

Interventions

We first established a case group that consisted of dogs treated with f-SCIT using allergens purchased from ALK in the first centre. This protocol had a shortened induction phase that lasted only four weeks (Table 1). The control group consisted of dogs treated with c-SCIT using ALK allergens at the second centre. In the c-SCIT group, the AIT protocol, done according to the manufacturer's recommendations, included a long induction phase with three vials of increasing allergen concentrations in an aqueous solution injected over a period lasting up to 20 weeks (Table 1). In both centres located in the northeastern United States, most patients were polysensitized and experienced year-round clinical signs with or without seasonal exacerbations. Allergen testing was done throughout the year, preferentially in the season of allergy flares. Generally, the allergen selection for SCIT was based on allergens deemed positive by intradermal $\pm$ immunoglobulin (Ig)E serological tests; the AIT was started shortly after the results of the tests were available.

A dermatological technician gave the first SCIT injection in-clinic, and dogs were monitored for 30min. All other injections were given at home by the owner. At the appointment when the first injection was given, the owners were educated about the expected AEs (e.g. a mild increase in itch after the injections), and were instructed to contact the dermatologist immediately in case of AE development. Furthermore, clinic-specific handouts about AEs were given to all clients. Re-evaluation visits at both centres were scheduled every two

to four months after starting the SCIT. At these re-evaluations, the tolerance to SCIT injections was discussed and owners were questioned about any signs of AEs.

Study subjects

We included dogs diagnosed with AD in the two specialty clinics based on the following criteria.

Inclusion criteria:

- AD diagnosed based on classic clinical signs and exclusion of other pruritic skin diseases; and,
- An age of AD onset between six months and 5 years; and,
- A routine flea and tick prevention; and,
- A SCIT based on results from allergen-specific IgE serology or intradermal test; and,
- A follow-up until the first re-evaluation after reaching the AIT maintenance phase.

Exclusion criteria:

- Presence of sole atopic otitis, urticaria or angioedema; or,
- Signs of AD controlled solely with a diet change; or,
- SCIT with mold-containing multiple vials

Anti-allergic treatment

For all dogs, anti-allergic medications were prescribed by the specialists and were kept unchanged during the induction phase. Their use was recorded based on medical records, prescription and billing information of the specialty clinics. Over-the-counter medications such as H1R antihistamines were added based on medical records. As anti-allergic medication can reduce type I hypersensitivity reactions, we pre-planned two subgroups of subjects. The treatment subgroup I (TS1, i.e. "noninterfering treatment") encompassed dogs receiving recommended or approved dosages of anti-allergic drugs already shown not to reduce type I hypersensitivity reactions such as intradermal histamine injections.^{22–24} These drugs were ciclosporin, oclacitinib and lokivetmab used alone or in combination. The second subgroup (TS2, i.e. "interfering treatment") was composed of dogs receiving anti-allergic drugs known to reduce intradermal histamine reactions. In TS2, we included oral glucocorticoids and H1R antihistamines,²⁴ and did not include topical glucocorticoids that were used as needed on a limited body surface area, as precise data on the frequency of application, the area treated and amount used were usually missing.

Table 1. Comparison between the ALK (ALK-Abello; Round Rock, TX, USA) fast-escalation subcutaneous immunotherapy (f-SCIT) and ALK conventional (c-SCIT) protocols

	Fast-escalation SCIT		Conventional SCIT					
	Vial 3		Vial 1		Vial 2		Vial 3	
	Day	mL	Day	mL	Day	mL	Day	mL
Induction	0	0.10	3–4	0.10	25–35	0.05	60–92	0.05
	7	0.20	6–8	0.20	29–42	0.10	67–100	0.10
	14	0.40	9–12	0.30	33–49	0.20	74–108	0.20
	21	0.80	12–16	0.40	37–56	0.35	81–116	0.35
	28	1.00	15–20	0.55	41–63	0.50	88–124	0.50
			18–24	0.70	45–70	0.60	95–132	0.60
			21–28	0.85	49–77	0.70	102–140	0.70
					53–84	0.85		
Maintenance vial 3	q 14d	1.00					q 14–21d	0.75
Maintenance reached (day)		28						102–140

ALK SCIT is an aqueous solution with 0.4% phenol. Vial 1: 100–200 PNU, 1:20,000 w/v; Vial 2: 1,000–2,000 PNU, 1:2,000 w/v; Vial 3: 10,000–20,000 PNU, 1:200 w/v.

d days, q every, w/v weight per volume.

Table 2. Grading scale for allergen immunotherapy (AIT)-induced local and systemic adverse events (AEs) in animals

Local adverse event (LR)	Systemic adverse event (SR)			
	Grade I	Grade II	Grade III	Grade IV
Localized cutaneous reaction	One organ system affected	More than one organ system affected OR any of the signs listed below	Anaphylaxis Any of the signs listed below, concurrent signs of grade I and II are possible	Death
localized pruritus at injection site	Cutaneous generalized pruritus	Cutaneous urticaria, flushing, angioedema (not oral)	Upper respiratory laryngeal, tongue oedema	
or swelling of injection site	or Upper respiratory rhinitis	or Lower respiratory cough, wheezing	or Lower or Upper respiratory respiratory failure	
or infection/abscess at injection site	cough or Conjunctival erythema, pruritus, tearing or Other lethargy, anorexia, nausea	Gastrointestinal vomiting, oedema	Cardiovascular hypotension, hypertension	

Medication scores

In order to normalize the accounting of anti-allergic drugs between dogs, we used the medication score (MS) proposed by Gonzales *et al.*⁴ In this scheme, 1 mg prednisone/prednisolone/methylprednisolone, 5 mg ciclosporin, 0.5 mg oclacitinib, 2 mg hydroxyzine and 1 mg cetirizine (all oral dosages per kg per day) were considered equivalent and worth one daily point. If ciclosporin was used in combination with ketoconazole, both daily dosages were added, and the sum was converted into points based on 5 mg/kg being equal to one point. To this scheme, we also considered 2 mg/kg lokivetmab every four weeks to be worth one daily point. The total MS for all drugs and each specific drug were calculated. The total MS for the anti-allergic medications was reported as daily averages for all drugs that the dogs received. If drugs were given only every other day or less frequently, the MS was divided by the number of days on which the medication was taken.

Adverse event classification

Adverse events of SCIT were recorded and graded during the induction phase of each SCIT protocol. We divided AEs into local (LR) and grade I–IV systemic reactions (SR), as first proposed by the World Allergy Organization.^{14,25,26} This scheme was modified as an easy-to-use tool for veterinary medicine and applied retrospectively to the reported AEs (Table 2).

Causality scale

We used the Modified Naranjo Causality Scale to provide a safety report (MONARCSI) score for each AE at each time to assess the probability of SCIT causation (Appendix S1).^{27,28} This score weighted and reformulated the 10 original Naranjo score questions and was considered more applicable to the situation in veterinary medicine.²⁸

Rates of adverse events

The primary outcome measures were the incidence and type of AEs in dogs of each SCIT treatment group. The secondary outcome measures were the proportion of AEs that were self-limiting (i.e. medications were not needed to treat the AE) or that led to a change in the AIT protocol (termination, injection frequency or dosing). Finally, we recorded the breed types and the body weights of dogs experiencing AEs to evaluate the potential risk for smaller dogs of developing SCIT reactions, as, for example, small-breed dogs appear to suffer from vaccine-induced ischaemic dermatopathies more than large-breed dogs.²⁹

Statistics.

As we hypothesized that the f-SCIT had a similar rate and grade of AEs than those of the c-SCIT protocol, we used two-tailed Fisher's exact tests to compare all categorical parameters between treatment regimens (<https://www.graphpad.com/quickcalcs/contingency2/>; page last accessed on April 30, 2020). Continuous data, like the age of the dogs and the medication scores for each of the treatment subgroups, were first tested for a normal distribution (<https://www.socscistatistics.com/tests/kolmogorov/default.aspx>; page last accessed on April 29, 2020) and compared, between the two treatment groups using a parametric, two-tailed Student's *t*-test for normally distributed data (<https://www.graphpad.com/quickcalcs/ttest1/>; page last accessed on April 30, 2020). When data were not normally distributed, we compared them with the two-tailed Wilcoxon–Mann–Whitney U-test (<https://www.socscistatistics.com/tests/mannwhitney/default2.aspx>; page last accessed on April 30, 2020). We defined the level of statistical significance as $P < 0.05$.

Results

Study subjects

We retrospectively included 100 dogs from two specialty centres. Fifty dogs each were treated with the ALK f-SCIT (Centre 1) or c-SCIT (Centre 2; details of all cases are shown in Appendix S2).

There were two notable differences between the two centers SCIT protocol groups. First, the mean age of the dogs receiving the c-SCIT was significantly higher compared to that of dogs from the f-SCIT group (two-tailed Wilcoxon–Mann–Whitney U-test; $P = 0.0018$). Secondly, there were fewer small-breed and more giant-breed dogs – and thus, a higher body weight – in the c-SCIT group than in the f-SCIT group (two-tailed unpaired Student's *t*-test; $P = 0.0014$, respectively) (Appendix S3).

Anti-allergic treatment and medication scores

In order to account for potential drug interference that could affect the rates of AEs, we compared the anti-allergic drugs prescribed during the SCIT induction phase between the two groups (Table 3). There were several noteworthy differences between them: first, the

Table 3. Numbers and percentages of dogs that received anti-allergic drug treatment during the subcutaneous immunotherapy (SCIT) induction phase, medication scores are listed for each treatment protocol (f-SCIT, fast-escalation; c-SCIT, conventional)

	Total #	Anti-allergic Tx # (%)	TS1 Noninterfering Tx MS	TS2 Interfering Tx # (%)	Oral glucocorticoids MS	H1R antihistamines # (%)	Oclacitinib MS	Ciclosporin # (%)	Lokivetmab MS	Topical glucocorticoids # (%)	MS	# (%)	MS	# (%)	MS	# (%)	MS	# (%)
f-SCIT	50	46 (92) a	1.0	40 (80) b	1.0	4 (8)	0.6	2 (4)	0.5	2 (4)	1.6	16 (32)	1.0 c	16 (32) d	1.1	11 (22)	1.0	7 (14)
c-SCIT	50	31 (62) a	1.2	21 (42) b	1.2	6 (12)	0.9	3 (6)	0.2	3 (6)	2.2	17 (34)	1.2 c	3 (6) d	1.2	4 (8)	1.0	11 (22)

Significance levels (*P*-values): a, 0.0006; b, 0.0002; c, 0.0200; d, 0.0017. Comparisons for oral glucocorticoids and H1R antihistamines were not made owing to a small number of dogs. Daily medication scores are shown as medians.

H1R type 1 histamine receptor, MS medication scores, TS treatment subgroup, Tx treatment.

proportions of dogs treated with either anti-allergic, “non-interfering” drugs or ciclosporin were significantly lower in the c-SCIT group (Table 3). Secondly, although the proportion of dogs receiving oclacitinib was similar between the two groups, on average, a significantly higher oclacitinib dose was prescribed in the c-SCIT group. Importantly, the proportion of dogs treated with drugs “interfering” with type I immediate allergic reactions and the medication score of TS2 drugs was not significantly different between the two groups ($P > 0.05$; unpaired Student's *t*-test for normally distributed data and Wilcoxon–Mann–Whitney U-test for nonparametric data).

Rates of adverse events

Altogether, 12 of 100 dogs (12%) experienced at least one reported SCIT-attributable AE during the induction phase (Table 4). Among these, there was one LR with focal pruritus at the injection site in a dog receiving f-SCIT. The other 11 reactions were SRs: nine were of Grade I and two of Grade II (Table 4); grade III-to-IV severe SRs were not observed.

The prevalence of AEs, that of SRs and that of Grade I SRs, was significantly higher in dogs receiving the f-SCIT than in those treated with the c-SCIT protocol (Table 4); in the latter group, LRs and Grade I SRs were not seen.

Using the MONARCSi causality scale, eight of 11 (73%) AEs in the f-SCIT group were considered “certain”, two of 11 (18%) “likely” or “likely-to-certain”, and one of 11 (9%) “plausible” (Appendix S4). Likewise, the single AE in the c-SCIT group was considered “likely”. The most common SR observed was increased generalized pruritus, with or without erythema, shortly after a SCIT injection (six of 11, 55%). The second most common AE was an acute erythematous dermatitis, often present on the ventrum (three of 11, 27%). Grade II reactions included swelling and erythema of the paws and the periocular area in combination with vomiting (one dog in the f-SCIT group) and acute vomiting 30 min after an injection in one dog in the c-SCIT group.

Of importance are the observations that all SRs were seen in dogs in the TS1 (“noninterfering treatment”) group, and that none of the dogs treated with oral glucocorticoids experienced any AE (Appendix S4). By contrast, topical glucocorticoids and H1R antihistamines did not prevent AEs, as two dogs treated with the former exhibited an SR, and the dog experiencing the single LR had received cetirizine (Appendix S4). Importantly, all reported reactions in the f-SCIT group were self-limiting, as they did not require any further treatment. The SR Grade II (vomiting) in the c-SCIT group was treated symptomatically.

The SCIT protocol was modified in 10 of 12 dogs (83%) after they experienced an AE, and this was done by a slower increase of the SCIT volume injected. In 11 of 12 dogs (92%), the final concentration of SCIT was reached. In the dog experiencing the Grade II SR in the f-SCIT group, the maintenance dose administered was half of the usual volume (Appendix S4). After experiencing a SCIT-attributable AE and a follow-up with the veterinarian, three dogs (all Grade I SR) in the f-SCIT group were prescribed a prophylactic treatment to prevent further AEs: oral H1R antihistamines were given the day before, the day of and the day after the injection and no additional AEs were noted.

We also evaluated whether small-breed dogs were at a higher risk of developing a SCIT-induced AE. The prevalence of AEs was not significantly different between dog breed types, as two of 15 (13%) small-, three of 31 (10%) medium- and six of 38 (15%) large-breed dogs had a SCIT-attributable AE ($P = 1.000$, two-tailed Fisher's exact test for all comparisons) (Appendix S3); none of the giant-breed dogs suffered an AE. The mean weight of dogs with an AE was 24 kg.

Discussion

In this case-control study the rate of AEs in the f-SCIT protocol (22%) was significantly higher compared to the c-SCIT (2%) group. Importantly, almost all AEs in dogs treated with the f-SCIT were mild (LR or Grade I SR) and self-limiting (nine of 10, 90%). Moreover, the single AE reported in dogs treated with the c-SCIT was a Grade II SR consisting of vomiting requiring treatment; this observation shows that the risk for severe systemic AEs is not eliminated by an extension of the induction phase of AIT.

In our study, the variation in the rate of total AEs between groups was similar to that historically reported for SCIT studies, ranging from 0.5 to 73%.^{4,9,17–21} Likewise, the AEs described herein are of a severity similar to those reported in the veterinary literature, with the majority of AEs being LRs or mild SRs with occasional cases of urticaria, angioedema and gastrointestinal AEs.^{4,9,17–21} We did not observe any severe grade III-to-IV SRs, and there is only one other publication that reports the occurrence of SCIT-induced anaphylaxis in a single dog.¹⁹ This reduced risk of severe reaction after SCIT in dogs should be contrasted with that in humans where AEs are more severe, and the fatality rate is 1:2–2.5 million injections. One explanation of the increased severity of AEs in humans undergoing AIT treatment compared to dogs might be the allergic disorder being treated. In people, AIT is infrequently used in patients with AD, by contrast

Table 4. Number of dogs, percentages and types of adverse events (AEs) reported during subcutaneous immunotherapy (SCIT) induction for each treatment protocol (f-SCIT, fast-escalation; c-SCIT, conventional)

	Total #	Total AEs # (%)	LR # (%)	Total SR # (%)	SR grade I # (%)	SR grade II # (%)	SR grade III-IV # (%)
f-SCIT	50	11 (22) a	1 (2)	10 (20) b	9 (18) c	1 (2)	0 (0)
c-SCIT	50	1 (2) a	0 (0)	1 (2) b	0 (0) c	1 (2)	0 (0)
Total	100	12 (12)	1 (1)	11 (11)	9 (9)	2 (2)	0 (0)

Significance level (*P*-values): a, 0.0038; b, 0.0078; c, 0.0026.

LR local reactions, SR systemic reactions.

to its recommendation for the prevention of the recurrence of signs of allergic rhinitis, asthma and insect venom hypersensitivities, in which usually more severe and often life-threatening clinical signs already are present in the disease being treated with AIT.^{30,31}

The advantages of this fast-escalation SCIT are the simplification of the induction protocol with a resulting potential improvement of the owners' adherence to therapy. The prescribed frequency of medications is known to affect the adherence to taking the drug or administering it to a dog.^{32,33} Even though most studies compared once-daily to multiple doses per day, we speculate that four weeks of weekly dose increases in the f-SCIT protocol should have a greater client adherence compared to the more complex and longer c-SCIT in which dosages are increased every three to seven days for three months. We expect that a longer induction phase should result in a lower adherence as a consequence of missed or delayed injections in the classic c-SCIT. In addition, the f-SCIT protocol might lead to a potential speeding up of the onset of AIT efficacy compared to more standard regimens. An assessment of the effectiveness of f-SCIT was not determined herein, yet it warrants further investigations.

In this study, and to help standardize the assessment of animal AIT-induced AEs in the future, we proposed the use of an AE scoring system modified from the World Allergy Organization.^{14,16,25,26} Besides this, we also selected a modified Naranjo score, as some questions in its original version were deemed not practical or relevant for veterinary medicine; for example, questions such as drug blood concentrations known to be toxic would never be scored positively, so the highest score would never be achieved. Similar questioning of the appropriateness of this drug probability was the reason behind the publication of the MODified NARAnjo Causality Scale that modified the 10 original questions and incorporated a different weighting for nine questions.^{27,28} In the present study, we used a medication score modified and expanded from that published previously to document the daily drug dosages received by the dogs.⁴ This scoring system, which is on a continuous scale, permitted greater precision in the grading of the drug used, by contrast to previously published scores that were more categorical and that we deemed less pertinent for our study.^{34,35}

A limitation of our approach was its retrospective design, which relied on owners for the detection and reporting of mild and self-limiting AEs; this could have led to missed AEs and incorrectly lower our estimation of the true incidence of AEs during any of the two SCIT protocols used. We attempted to limit confounding factors caused by our two center design by using clinics in the same geographical region, thus assuming them to have

the same dog population, the same seasons and the same AIT manufacturer. All SCIT injections were started in the same two-year time frame and the follow-up was provided by Dermatologists or dermatology residents. In spite of such similarities, we cannot exclude that differences between the two centers in the client communication and reporting of AEs might have occurred.

Another factor that may have affected the accuracy of our data involves the somewhat artificial classification of anti-allergy drugs as either "noninterfering" or "interfering", which was extrapolated from the inhibition potential of each drug on intradermal histamine injections.^{22–24} As such, dogs treated with drugs that inhibit pruritus such as lokivetmab, oclacitinib and ciclosporin, were grouped into the TS1 "noninterfering" treatment subgroup. Regrettably, there is no specific information to help us determine if, or to what extent, these drugs have the potential to inhibit or diminish the severity of AEs in SCIT-treated dogs. Nevertheless, as we identified dogs treated with each of these three drugs, or a combination thereof, that experienced grade I and II SRs such as generalized pruritus, it is unlikely that misclassification of these drugs in the wrong subgroup occurred. Finally, one could question the accuracy of the medication score used in this retrospective study. We relied on the pet owners to report the use and dosage of over-the-counter medication, such as antihistamines. However, as all prescription-requiring medications were approved by the specialty clinician, we could use the medical record, as well as the billing record, to provide accurate data about the medication prescribed and – hopefully – used by the pet owner.

In summary, we showed that a fast-escalating SCIT protocol led to the development of AEs in 22% of treated dogs, with mild and self-limiting signs occurring most often, sometimes as soon as the first or second injection. Accordingly, when using f-SCIT protocols, clients should be advised to monitor dogs closely for any mild increase in pruritus and erythema, and to report these to the dermatologist.

Even though the prevalence of AEs was higher in the f-SCIT group, the mild nature of these AEs and their ability to resolve spontaneously should prompt further studies to determine if this shortened protocol results in a faster time-to-benefit of AIT.

References

- Hoffmann HJ, Valovirta E, Pfaar O et al. Novel approaches and perspectives in allergen immunotherapy. *Allergy* 2017; 72: 1,022–1,034.
- Mueller RS, Jensen-Jarolim E, Roth-Walter F et al. Allergen immunotherapy in people, dogs, cats and horses – differences, similarities and research needs. *Allergy* 2018; 73: 1,989–1,999.

3. Nesbitt GH. Canine allergic inhalant dermatitis a review of 230 cases. *J Am Vet Med Assoc* 1978; 172: 55–60.
4. González JL, Zalve V, Fernández-Caldas E et al. A pilot study of immunotherapy in dogs with atopic dermatitis using a mannann-*Dermatophagoides farinae* allergoid targeting dendritic cells. *Vet Dermatol* 2018; 29: 449–e152.
5. Colombo S, Hill PB, Shaw DJ et al. Effectiveness of low dose immunotherapy in the treatment of canine atopic dermatitis: a prospective, double-blinded, clinical study. *Vet Dermatol* 2005; 16: 162–170.
6. 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: 167–173.
7. Fujimura M, Ishimaru H. Rush sublingual immunotherapy in canine atopic dermatitis: a prospective pilot study. *Pol J Vet Sci* 2016; 19: 3–6.
8. Timm K, Mueller RS, Nett-Mettler CS. Long-term effects of intra-lymphatic immunotherapy (ILIT) on canine atopic dermatitis. *Vet Dermatol* 2018; 29: 123–e49.
9. Plant JD, Neradilek MB. Effectiveness of regionally-specific immunotherapy for the management of canine atopic dermatitis. *BMC Vet Res* 2017; 13: 1–6.
10. Zur G, Ihrke PJ, White SD et al. Canine atopic dermatitis: a retrospective study of 266 cases examined at the University of California, Davis, 1992–1998. Part I. Clinical features and allergy testing results. *Vet Dermatol* 2002; 13: 89–102.
11. Schnabl B, Bettenay BV, Dow K et al. Results of allergen-specific immunotherapy in 117 dogs with atopic dermatitis. *Vet Rec* 2006; 158: 81–85.
12. Nuttall TJ, Thoday KL, Van den Broek AHM et al. Retrospective survey of allergen immunotherapy in canine atopy. *Vet Rec* 1998; 143: 139–142.
13. Calderón MA, Vidal C, Rodríguez del Río P et al. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. *Allergy* 2017; 72: 462–472.
14. Cox L, Larenas-Linnemann D, Lockey RF et al. Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol* 2010; 125: 569–574.
15. Cox L, Nelson H, Lockey R et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; 127: S1–S5.
16. Epstein TG, Liss GM, Murphy-Berendts K et al. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008–2012: an update on fatal and nonfatal systemic allergic reactions. *J Allergy Clin Immunol Pract* 2014; 2: 161–167.
17. Willemse A, Van den Brom WE, Rijnberk A. Effect of hyposensitization of atopic dermatitis in dogs. *J Am Vet Med Assoc* 1984; 184: 1,277–1,280.
18. Willemse T, Bardagi M, Carlotti DN 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: 337–342.
19. Rosser EJ. Aqueous hyposensitization in the treatment of atopic dermatitis: a retrospective study of 100 dogs. In: Kwochka KW, Willemse T, von Tscherner C eds. *Advances in Veterinary Dermatology*, volume 3. Oxford: Butterworth Heinemann, 1998; 169–176.
20. Kovše M, Zrimšek P, Kotnik T. Evaluation of the effect of allergen-specific immunotherapy in atopic dogs using the CADESI-03 scoring system: a methylprednisolone- controlled clinical study. *Vet Arhiv* 2012; 82: 251–264.
21. Briand A, Prelaud P, Cochet-Faivre N et al. Safety evaluation of allergen specific immunotherapy without an induction phase using calcium phosphate adjuvanted allergenic extracts in atopic dogs: a retrospective study of one hundred eighty five cases. *Int J Appl Res Vet Med* 2018; 16: 203–210.
22. Souza CP, Rosychuk RAW, Contreras ET et al. A retrospective analysis of the use of lokivetmab in the management of allergic pruritus in a referral population of 135 dogs in the western USA. *Vet Dermatol* 2018; 29: 489–e164.
23. Clear V, Peterson A, Rosser EJJ et al. Investigation of the effects of 30 day administration of oclacitinib on intradermal and allergen-specific IgE serology testing in atopic dogs. *Vet Dermatol* 2015; 26: 148 (abstract).
24. Olivry T, Saridomichelakis M. Evidence-based guidelines for anti-allergic drug withdrawal times before allergen-specific intradermal and IgE serological tests in dogs. *Vet Dermatol* 2013; 24: 225–e49.
25. Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization systemic allergic reaction grading system: Is a modification needed? *J Allergy Clin Immunol Pract* 2017; 5: 58–62.
26. Passalacqua G, Baena-Cagnani CE, Bousquet J et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language. *J Allergy Clin Immunol* 2013; 132: 93–98.
27. Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239–245.
28. Comfort S, Dorrell D, Meireis S et al. MODified NARANJO Causality Scale for ICSRs (MONARCSI): a decision support tool for safety scientists. *Drug Saf* 2018; 41: 1,073–1,085.
29. Backel KA, Bradley CW, Cain CL et al. Canine ischaemic dermatopathy: a retrospective study of 177 cases (2005–2016). *Vet Dermatol* 2019; 30: 403–e122.
30. Weidinger S, Beck LA, Bieber T et al. Atopic dermatitis. *Nat Rev Dis Prim* 2018; 4: 1.
31. Jutel M, Agache I, Bonini S et al. International consensus on (ICON) allergy immunotherapy (AIT). *J Allergy Clin Immunol* 2015; 136: 556–568.
32. Adams VJ, Campbell JR, Waldner CL et al. Evaluation of client compliance with short-term administration of antimicrobials to dogs. *J Am Vet Med Assoc* 2005; 226: 567–574.
33. Coleman CI, Limone B, Sobieraj DM et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm* 2012; 18: 527–539.
34. Mueller RS, Fieseler KV, Fettman MJ et al. Effect of omega-3 fatty acids on canine atopic dermatitis. *J Small Anim Pract* 2004; 45: 293–297.
35. Fischer N, Tarpataki N, Leidi F et al. An open study on the efficacy of a recombinant Der f 2 (*Dermatophagoides farinae*) immunotherapy in atopic dogs in Hungary and Switzerland. *Vet Dermatol* 2018; 29: 337–e118.

Supporting Information

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

Appendix S1. MONARCSI score questions and calculation method for final MONARCSI scores.

Appendix Table S2. Primary data of study subjects.

Appendix Table S3. Age, weight, breed characteristics, prevalence of total SR and SR grade II per breed class of dogs treated with AIT.

Appendix Table S4. Characteristics of adverse events.

Résumé

Contexte – L'immunothérapie allergénique (AIT) est le seul moyen supposé capable de changer l'évolution des maladies atopiques. Les chiens semblent avoir peu d'effets secondaires (AEs) comparé à l'homme, une phase d'induction à doses croissantes pourrait être inutile.

Objectifs – Décrire l'incidence et les caractéristiques des AEs dus à l'immunothérapie sous cutanée à induction rapide (f-SCIT) comparé à un traitement conventionnel (c-SCIT).

Sujets – Cent chiens traités soit par f-SCIT (Centre 1, 50 chiens) ou c-SCIT (Centre 2, 50 chiens).

Matériels et méthodes – Une étude contrôle rétrospective évaluant les AEs au cours de l'induction de AIT. Nous avons déterminé l'incidence et le type d'AEs dans chaque groupe SCIT ; nous déterminons aussi les facteurs tels que la guérison spontanée et le besoin de changer les protocoles associés aux AE.

Résultats – Douze des 100 chiens (12%) ont développés des AE attribuables à SCIT au cours de la phase d'induction, avec réaction locale chez un chien et réactions systémiques chez 11 chiens (neuf Grade I, deux Grade II, aucun grades III ou IV). Les chiens traités avec f-SCIT avaient un taux significativement plus élevé d'AEs (11 sur 50; 22%) comparé à ceux recevant c-SCIT (un sur 50; 2%). La plupart des AEs (10 sur 11; 91%) dans le groupe f-SCIT étaient modérés et spontanément contrôlés.

Conclusions et importance clinique – La phase d'induction de f-SCIT est simple et la phase de maintenance est atteinte plus rapidement que celle de c-SCIT. Malgré leur taux élevé, la majorité des AEs associés à f-SCIT étaient modérés et auto-résolutifs. Il faut encore déterminer si ce protocole mène à une efficacité clinique plus rapide.

RESUMEN

Introducción – la inmunoterapia con alérgenos (AIT) es la única intervención que se cree que cambia el curso de las enfermedades atópicas. Dado que los perros parecen tener menos eventos adversos graves (AEs) en comparación con las personas que reciben AIT, es posible que no sea necesaria una fase de inducción de aumento de dosis prolongada.

Objetivos – reportar la incidencia y las características de los AEs inducidas por un protocolo de inmunoterapia subcutánea escalonada rápida (f-SCIT) en comparación con un régimen convencional (c-SCIT).

Animales – Cien perros tratados con f-SCIT (Centro 1, 50 perros) o c-SCIT (Centro 2, 50 perros).

Métodos y materiales – un estudio de casos con controles que evaluó retrospectivamente los AEs durante la inducción de la AIT. Determinamos la incidencia y el tipo de AEs en cada grupo de SCIT; también evaluamos factores como la autolimitación y la necesidad de cambios de protocolo asociados a AEs.

Resultados – doce de 100 perros (12%) desarrollaron un AE atribuible a SCIT durante la fase de inducción, con un perro con reacciones locales y 11 con reacciones sistémicas (nueve de grado I, dos de grado II, ninguno de grado III o IV). Los perros tratados con f-SCIT tuvieron una tasa significativamente mayor de AEs (11 de 50; 22%) en comparación con los que recibieron c-SCIT (uno de 50; 2%). La mayoría de los AEs (10 de 11; 91%) en el grupo de f-SCIT fueron leves y autolimitantes.

Conclusiones e importancia clínica – la fase de inducción de la f-SCIT es más simple y la fase de mantenimiento se alcanza más rápido que con la c-SCIT. A pesar de su mayor tasa de AEs que con el régimen de c-SCIT, la mayoría de los AEs asociados con la f-SCIT fueron leves y autolimitantes. Se debe determinar si este protocolo f-SCIT induce tratamiento efectivo más rápido.

Zusammenfassung

Hintergrund – Die Allergenimmuntherapie (AIT) ist die einzige Intervention, von der man glaubt, dass sie den Verlauf der atopischen Erkrankung beeinflussen kann. Da Hunde scheinbar weniger Nebenwirkungen (AEs) als Menschen, die AIT erhalten, haben, könnte es möglich sein, dass eine verlängerte Dosis-Eskalations Induktionsphase nicht benötigt wird.

Ziele – Ein Bericht über das Auftreten und die Charakteristika der AEs, die durch das Protokoll einer subkutanen Schnell-Eskalations Immuntherapie (f-SCIT) im Vergleich zu einem konventionellen (c-SCIT) Regime ausgelöst werden.

Tiere – Einhundert Hunde, die entweder mit f-SCIT (Zentrum 1, 50 Hunde) oder c-SCIT (Zentrum 2, 50 Hunde) behandelt wurden.

Methoden und Materialien – Eine Fall-Kontrollstudie, die retrospektiv die AEs während der Induktionsphase des AIT evaluierte. Wir bestimmten die Häufigkeit und den Typ der AEs einer jeden SCIT Gruppe; wir erfassten ebenso Faktoren wie Selbst-Limitierung und den Bedarf einer AE-assoziierten Protokolländerung.

Ergebnisse – Zwölf von 100 Hunden (12%) entwickelten SCIT-zuordenbare AEs während der Einleitungsphase, wobei ein Hund eine lokale und 11 eine systemische Reaktion hatten (neun Grad I, zwei Grad II, keine Grad III oder IV). Hunde, die mit einer f-SCIT behandelt wurden, hatten eine signifikant höhere Rate an AEs (11 von 50; 22%) im Vergleich zu jenen, die c-SCIT erhielten (einer von 50; 2%). Die meisten AEs (10 von 11; 91%) in der f-SCIT Gruppe waren mild und selbstlimitierend.

Schlussfolgerungen und klinische Bedeutung – Die Einleitungsphase von f-SCIT ist einfacher und die Erhaltungsphase wird rascher erreicht als mit c-SCIT. Trotz der höheren Zahlen an AEs mit dem c-SCIT Regime, waren die Mehrheit der f-SCIT-assoziierten AEs mild und selbstlimitierend. Ob das f-SCIT Protokoll zu einem rascheren Wirkungseintritt führt, muss noch bestimmt werden.

要約

背景 – アレルゲン免疫療法 (AIT) は、アトピー性疾患の推移を変えると考えられている唯一の介入である。犬はAITで治療している人と比較して重篤な有害事象 (AE) が少ないように見えるため、長期用量漸増誘導期は必要ない可能性がある。

目的 – 本研究の目的は、従来の (c-SCIT) レジメと比較した、急速段階的な皮下免疫療法 (f-SCIT) プロトコルによって引き起こされるAEの発生率と特性を報告することであった。

被験動物 – f-SCIT (センター1、50頭) またはc-SCIT (センター2、50頭) のいずれかで治療された100頭の犬。

材料と方法 – 本研究はAIT誘発中のAEを遡及的に評価する症例対照研究であった。各SCIT群のAE発生率および種類を決定した。また、自己制限やAE関連のプロトコル変更の必要性などの要因も評価した。

結果 – 犬100頭のうち12頭 (12%) が導入期にSCITに起因したAEを発症し、そのうち1頭が局所反応を示し、11頭が全身反応を示した (グレードIが9頭、グレードIIが2頭、グレードIIIまたはIVのいずれもなし)。f-SCIT治療犬 (50頭のうち11頭; 22%) は、c-SCIT治療犬 (50頭のうち1頭; 2%) と比較して、有意に高いAE率を示した。f-SCIT群のほとんどのAE (11頭のうち10頭; 91%) は軽度で自己制限的であった。

結論と臨床的重要性 – f-SCITの導入期はc-SCITよりも単純で、維持期に早く到達する。c-SCITレジメよりもAEの発生率が高いにもかかわらず、f-SCIT関連のAEの大部分は軽度で自己制限的であった。本研究のf-SCITプロトコルが、より早期の有効性につながるかどうかを判断する必要がある。

摘要

背景 – 過敏原免疫治療 (AIT) は唯一被认为改变异位性疾病病程的疗法。与接受AIT的病人相比，犬的严重不良反应 (AEs) 似乎较少，因此可能不需要长时间的剂量递增诱导期。

目的 – 报告与传统 (c-SCIT) 方案相比，快速递增皮下免疫治疗 (f-SCIT) 方案诱导的AE发生率和特征。

动物 – 100只犬接受f-SCIT (中心1, 50只犬) 或c-SCIT (中心2, 50只犬) 给药。

方法和材料 – 回顾性评价AIT诱导期间AE的病例对照研究。我们确定了每个SCIT组中AE的发生率和类型；我们还评估自限性和AE相关方案变更需求等因素。

结果 – 100只犬中有12只 (12%) 在诱导阶段发生SCIT引起的AE，其中1只犬出现局部反应，11只犬出现全身反应 (9只为I级，2只为II级，无III级或IV级反应)。接受f-SCIT治疗的犬的AE发生率 (11/50; 22%) 显著高于接受c-SCIT治疗的犬 (1/50; 2%)。f-SCIT组的大多数AE (10/11; 91%) 是轻度和自限性的。

结论和临床重要性 – f-SCIT的诱导期更简单，且比c-SCIT更快达到维持期。尽管其AE发生率高于c-SCIT方案，但大多数f-SCIT相关AE是轻度和自限性的。需要确定该f-SCIT方案的起效时间是否更快。

Resumo

Contexto – A imunoterapia com alérgenos (ITA) é a única intervenção em que se acredita que seja possível modificar curso das doenças atópicas. Como os cães parecem apresentar menos eventos adversos graves (EAs) em comparação com pessoas que recebem ITA, uma fase de indução com escalonamento de dose prolongada pode não ser necessária.

Objetivos – Relatar a incidência e as características dos EAs induzidos por um protocolo de imunoterapia subcutânea de escalonamento rápido (f-SCIT) em comparação com um regime convencional (c-SCIT).

Animais – Cem cães tratados com f-SCIT (Centro 1, 50 cães) ou c-SCIT (Centro 2, 50 cães).

Métodos e materiais – Um estudo de caso-controle avaliando retrospectivamente EAs durante a indução de ITA. Determinamos a incidência e o tipo de EAs em cada grupo SCIT; também avaliamos fatores como autolimitação e a necessidade de mudanças no protocolo associado ao EA.

Resultados – Doze de 100 cães (12%) desenvolveram um EA atribuível à SCIT durante a fase de indução, com um cão tendo uma reação local e 11 tendo reações sistêmicas (nove Grau I, dois Grau II, nenhum dos graus III ou IV). Os cães tratados com o f-SCIT tiveram uma taxa significativamente maior de EAs (11 de 50; 22%) em comparação com aqueles que receberam o c-SCIT (um de 50; 2%). A maioria dos EAs (10 de 11; 91%) no grupo f-SCIT foram leves e autolimitados.

Conclusões e importância clínica – A fase de indução do f-SCIT é mais simples, e a fase de manutenção é alcançada mais rapidamente que a do c-SCIT. Apesar de sua taxa mais alta de EAs do que com o regime c-SCIT, a maioria dos EAs associados à f-SCIT foram leves e autolimitados. Se este protocolo f-SCIT leva ou não a um tempo de eficácia mais rápido, precisa ser determinado.

Supplementary Material 1: listed are the modified MONARCSi score questions used in our study and information about grading and calculation of the final MONARCSi score

MONARCSi causality scale: Questionnaire adapted to SCIT-induced AEs in dogs

Fill in “Y” for “Yes”, “N” for “No” or “NA” for “not applicable/unknown” for the questions 1-9, and summarize the AEs in the question 9.

1. Is this adverse event consistent with a significant safety event associated with SCIT use?
2. Are there previous reports of this adverse reaction with SCIT, which support a causal relationship?
3. Is the adverse event onset temporally associated the use of SCIT?
4. Is the adverse event consistent with the mechanism of action of SCIT?
5. Did the adverse event resolve or improve when the SCIT was discontinued?
6. Did the adverse event recur when the SCIT was re-administered?
7. Was the adverse event affected by dosing changes, either an increase or a decrease?
8. Are other data present that support a causal relationship (e.g., repeatable AEs)?
9. Are there alternative explanatory causes or confounding factors for the adverse event present?

MONARCSi causality scale: Grading and interpretation³³

For each question, “yes”, “no” and “not applicable/unknown” are translated into +1, -1 and 0, respectively. These numbers are multiplied with the weighting matrix (published in ref. 33) for each question resulting in a total mean MONARCSi score (Sm) with a standard deviation (SD). This score including the SD is translated to a probability of causal relationship ranging from 0 to 1 based on a fitted logistic equation;

$\text{Prob (Sm)} = 1/[1 + \exp(-(-0.67 + 0.36 \times \text{Sm}))]$ (courtesy of S. Comfort – see reference 33).

The probability of causal relationship score is applied to a classification with distinct categories: *excluded* [0.00 - 0.05], *unlikely* [0.06 - 0.25], *doubtful* [0.25 - 0.45], *intermediate* [0.45 - 0.55], *plausible* [0.55 - 0.75], *likely* [0.75 - 0.95], or *certain* [0.95 - 1]. Taking into consideration the SDs, overlapping categories are possible (e.g., *likely-to-certain*).³³

Supplementary Material 4: Characteristics of adverse events, listed are the anti-allergic medication, the MONARCSi score, the self-limiting character of the AE, changes in the SCIT induction protocol, prophylactic treatment used to prevent further AEs and maximum recommended SCIT dose reached for all AE events grouped based on AE grade

		LR	SR Grade I		SR Grade II	
		f-SCIT	f-SCIT	c-SCIT	f-SCIT	c-SCIT
Total #		1	9	0	1	1
TS1 Non-interfering Tx (%)		0	8 (89)		1 (100)	1 (100)
	Topical GCs		1			1
	CSA [MS]		4 [1.1]			
	OCL [MS]		2 [0.9]		1 [1.1]	1 [1.2]
	LKV [MS]		2 [0.7]			
TS 2 Interfering Tx (%)		1 (100)	0		0	0
	H1RA [MS]	1 [0.7]				
No concurrent Tx			1 (11)		0	0
MONARCSi score	Certain (%)	1 (100)	6 (67)		1 (100)	0
	Likely (%)		2 (22)		0	1 (100)
	Plausible (%)		1 (11)		0	0
Self-limiting AEs	Yes (%)	1 (100)	9 (100)		1 (100)	1 (100)
	No (%)		0		0	0
Change in SCIT protocol	Yes (%)		9 (100)		1 (100)	0
	No (%)	1 (100)	0		0	1 (100)
Prophylactic Tx used	Yes (%)		3 (33)		0	0
	No (%)	1 (100)	6 (67)		1 (100)	1 (100)
Max. SCIT dose reached	Yes (%)	1 (100)	9 (100)		0	1 (100)
	No (%)		0		1 (100)	0

Daily medication score is shown as median

Abbreviations: CSA: ciclosporin; GCs: glucocorticoids; H1R: type 1 histamine receptor; LKV: lokivetmab; MS: medication scores; OCL: oclacitinib; TS: treatment subgroup; Tx: treatment

Supplementary Material 3: Age, weight and breed characteristics of dogs treated with AIT, prevalence of total SR and SR grade II per breed class were calculated and compared between the four breed classes

	Total #	Age		Body weight (kg)		Total dogs per breed class				Total SR AEs				SR Grade II			Mean weight (kg) of dogs with AEs
		Mean	Range	Mean	Range	Small	Medium	Large	Giant	Small	Medium	Large	Giant	Small	Medium	Large	
f-SCIT	50	4.2 a	2-12	23 b	4-58	13 c	14	20	3 d	2	3	5	0	1	0	0	23
c-SCIT	50	5.7 a	2-12	32 b	8-69	2 c	17	18	13 d	0	0	1	0	0	0	1	32
Total (%) [mean]	100	[5.0]	2-12	[27]	4-69	15 (15)	31 (31)	38 (38)	16 (16)	2 (13)	3 (10)	6 (15)	0	1 (7)	0 (0)	1 (5)	[24]

Significance levels (*P* value): a: 0.0018 b: 0.0014 c: 0.0038; d: 0.0122

Bodyweight classes are: Small 0-10 kg; Medium 11-25 kg, Large 26-39 kg and Giant > 40 kg

Abbreviations: AEs: adverse events; SR: systemic reaction