

Determination of the efficacy rate and time-to-efficacy of subcutaneous immunotherapy in dogs with atopic dermatitis

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Abstract

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Background

Allergen-specific immunotherapy (ASIT) is reported to have a success rate of 50–70% when given for up to 12 months to dogs with atopic dermatitis (AD). How soon ASIT is clinically effective is unclear.

Objectives

To compare the efficacy rate (ER) and time-to-efficacy (TTE) of various types of subcutaneous immunotherapy (SCIT) administered using conventional dosing regimens using the methodology of a critically appraised topic.

Methods and materials

Three databases were searched to extract information on the ER and TTE of SCIT in dogs with AD. Herein, “efficacy” was defined as a $\geq 50\%$ reduction in pruritus and/or skin lesions, and the TTE as the time needed to achieve such a reduction.

Results

We selected 12 publications including 194 dogs. The ER was significantly higher with the polymerised allergoids coupled with nonoxidized mannan than for the “classic” aqueous and alum-precipitated SCIT types. A TTE of three months or shorter was seen in a significantly higher proportion of dogs receiving mannan-couple allergoids, pullulan-conjugated Der f 2 or tyrosine-adjuvanted than aqueous or alum-precipitated SCIT; with the latter two formulations, the TTE might be nine months or longer in $\leq 20\%$ of atopic dogs.

Conclusions and clinical relevance

In spite of the low number of articles available for review and small number of enrolled dogs, novel SCIT regimens appear to have a faster – and possibly higher – efficacy than the currently available aqueous or alum-precipitated formulations. A standardisation of outcome measures for ASIT clearly is needed to allow a more meaningful comparison between SCIT types.

Introduction

Canine atopic dermatitis (AD) is one of the most common allergic skin diseases presented to both general practitioners and referral clinicians.¹ The management of this disease requires a multimodal approach that often will involve the combination of anti-allergic drugs (e.g. glucocorticoids, oclacitinib, ciclosporin), biologicals (e.g. lokivetmab) and/or allergen-specific immunotherapy (ASIT). The latter intervention is a safe treatment for canine AD² with a response (efficacy) rate reported to be between 50% and 70% (see review).³ The onset of clinical benefit [i.e. the time-to-efficacy (TTE) or response time] of ASIT in atopic dogs is expected to be slower than that of the aforementioned anti-allergic drugs and biologicals.² That there is a slower response of immunotherapy is supported by a recent report suggesting that ASIT lasting longer than one year was more effective than shorter treatment durations.⁴

At this time, however, there is no clear information on the comparative efficacy rate (ER) and TTE following various types of ASIT in atopic dogs. Knowing such parameters would aid in a comparison of immunotherapy protocols and assist veterinarians and pet owners in understanding how long a dog would need to receive anti-allergic drugs while waiting for a clinical benefit from ASIT.

Hypothetical clinical scenario

You diagnose a dog with AD. After determining its sensitisation pattern with an allergen-specific immunoglobulin (Ig)E serology, you propose treatment of this dog with subcutaneous immunotherapy (SCIT) using a conventional dosing regimen with aqueous allergens. The dog's owner asks you how long it will take before seeing that this treatment is effective.

Structured question

In a dog with AD, how long does it take for SCIT to have a $\geq 50\%$ reduction in clinical signs (pruritus and/or skin lesions)?

Materials and methods

Search strategy

We last searched the PubMed, Web of Science Core Collection and CAB Abstract databases on May 10, 2021, with the following sensitive Boolean query string: (dog or dogs or canine) and ((atopic or atopy) and dermatitis) and (immunotherapy or desensitization or hyposensitization)). There were no restrictions for publication dates or languages; conference abstracts or review papers were excluded.

Search for and identification of evidence

Altogether, our search yielded 781 different articles (see Supporting information Appendix [S1](#)). For the purpose of this report, we considered only SCIT that was allergen-specific and administered using conventional protocols (i.e. a slow and progressive dose-escalation “induction” period followed by a fixed-dose maintenance phase) to dogs with spontaneously arising AD. Additionally, publications must have had objective data permitting the determination of the TTEs, which we defined as the time when a $\geq 50\%$ reduction in pruritus and/or skin lesions was stably obtained. Finally, when a moderate or partial improvement of signs was reported in the studies, the definition of such terms had to be specified clearly.

Outcome measures

Herein, we defined “efficacy” as a $\geq 50\%$ reduction in pruritus, or skin lesions, or both, and the efficacy rate (ER) as the percentage of dogs in which SCIT had led to such an efficacious response. Whenever possible, we calculated the TTE for pruritus (TTE-p), skin lesions (TTE-l) or both (TTE-pl), and then grouped all studies based on the type of SCIT.

Statistics

The ERs and proportions of dogs with TTEs of three months or shorter duration were compared between SCIT types using a two-tailed Fisher’s exact tests (PRISM, Graphpad software; San Diego, CA) with significance established at 5%.

Results

Search strategy

Our search identified 781 articles of which we assessed 36 articles for their eligibility. We finally excluded 24 papers for reasons listed in Appendix [S1](#).

Altogether, we selected 12 publications including 194 dogs and 137 “responders” (71%),⁵⁻¹⁶ which included information permitting the determination of TTEs for pruritus, skin lesions or both. Studies were reported from 1984¹⁶ to 2021;^{8,9} all were in English except for one in German⁶ (Table [S1](#)).

As not all studies used a similar definition and/or description of pruritus and skin lesions, the author-chosen parameters are provided as Table [S2](#).

Efficacy rate

The ERs were 67% (35 of 51), 65% (53 of 82), 79% (22 of 28), 100% (16 of 16) and 65% (11 of 17) for the aqueous, alum-precipitated (AP), Der f 2-pullulan (Der f 2-P), polymerised allergoids coupled to a nonoxidized mannan (PAM) and tyrosine adjuvanted (TA)-based SCIT, respectively. The ER for PAM-SCIT was significantly higher than that of aqueous (Fisher's exact test; $P = 0.008$), AP ($P = 0.025$) and TA-SCIT ($P = 0.018$); the ER of was not significantly different between all other SCIT types.

Time to observation of a $\geq 50\%$ reduction in pruritus (TTE-p)

Five articles^{6, 10-13} had the relevant information needed to calculate the TTEs based on this clinical sign. In these, 14 of 28 (50%), seven of 16 (44%) and seven of 17 (41%) dogs treated with Der f 2-P,^{11, 12} PAM¹⁰ and TA-SCIT⁶ had had a $\geq 50\%$ reduction in pruritus (TTE-p) within three months, respectively (Figure 1; Table S2a). In other dogs treated with AP, PAM and TA-SCIT, TTE-p of six and nine month duration were needed (Table S3a). The percentage of dogs in which the TTE-p was three months or shorter was significantly higher for Der f 2-P ($P < 0.0001$), PAM ($P < 0.0001$) and TA ($P = 0.0006$) compared to AP-based SCIT.

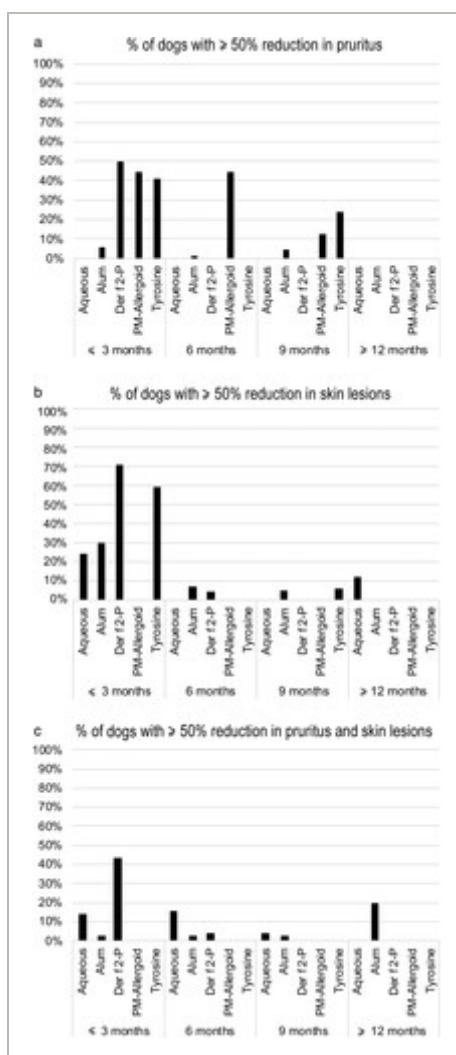


Figure 1

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Percentage of dogs with a $\geq 50\%$ reduction in pruritus (a), skin lesions (b) or both (c).

Time to observation of a $\geq 50\%$ reduction in skin lesions (TTE-l)

Nine publications^{5-9, 11-13, 15} had usable data to calculate this outcome measure. A $\geq 50\%$ reduction in skin lesions was achieved within three months in 20 of 28 (71%) and 10 of 17 (59%) dogs injected with Der f 2-P^{11, 12} and TA-based SCIT,⁶ respectively (Figure 1; Tables S3b). By contrast, a TTE of three months or shorter was seen in 25 of 82 (30%) and 12 of 51 (24%) dogs receiving AP and aqueous-based SCIT, respectively. A longer TTE was needed for all other dogs and, in six of 51 dogs (12%) injected with aqueous SCIT,⁵ the TTE was 12 months or longer (Table S2b). The percentage of dogs in which the TTE-l was three months or shorter was significantly higher for the Der f 2-P and TA than the aqueous and AP-based SCIT ($P < 0.001$ for comparisons with Der f 2-P; $P < 0.05$ for comparisons with TA).

Time to observation of a $\geq 50\%$ reduction in pruritus and skin lesions (TTE-pl)

Two papers (one with aqueous and the other AP-SCIT) reported the outcome as a combination of pruritus and skin lesions.^{14, 16} We also included three other articles that reported data on pruritus and skin lesions separately, as figures allowed the calculation of the TTE-pl.¹¹⁻¹³ Altogether, a $\geq 50\%$ reduction in pruritus and skin lesions within three months was achieved in 43% (12 of 28) of dogs receiving Der f 2-P,^{11, 12} and only 14% (seven of 51) of dogs that received aqueous-based SCIT, respectively (Figure 1; Table S3c).¹⁴ A similar outcome was seen at six and nine months in 16% (eight of 51) and 4% (two of 51) of dogs treated with aqueous SCIT.¹⁴ Finally, TTE-pl were reached in 2% (two of 82), 4% (three of 82) and 20% (16 of 82) of dogs injected with AP-SCIT for six, nine and 12 months or longer, respectively.^{13, 16} Altogether, the proportion of dogs having a TTE-pl of three months or shorter was higher for Der f 2-P and aqueous than AP-based SCIT ($P < 0.0001$ and 0.027, respectively).

Discussion

Implication for practitioners

Despite the low number of articles available for review and small number of enrolled dogs, the novel ASIT regimens (Der f 2-P, PAM, TA) appear to have a similar-to-higher ER, and a shorter time to clinically-relevant reductions in pruritus and/or skin lesions, than the currently available aqueous and AP-based SCIT. With these novel formulations, the efficacy is often seen by three months post initiation. This faster response might be a consequence of higher amounts of relevant allergens (especially for Der f 2-P) and/or the use of better adjuvants (e.g. mannan, pullulan). Because the TTE with current aqueous and AP regimens is

highly variable, veterinarians utilising SCIT to manage dogs with AD should perform frequent progress re-evaluations (at least every three months) to assess its efficacy and to determine the optimal time to taper or stop concurrent anti-allergic therapy.

Limitations

Several factors limit the interpretation of our data. First, despite decades of widespread practice of ASIT in atopic dogs, there was an astonishingly low number of studies – and dogs enrolled therein – reporting information usable for TTE determination. Secondly, the TTE of SCIT likely is influenced by the concurrent use of anti-allergic pharmaceutical interventions, yet few studies reported a medication score and its variation over time. Indeed, a short TTE could be the result of an aggressive anti-allergic therapy, whereas a longer one could result from suboptimal symptomatic therapy; we did not find any indication of differing anti-allergic treatment prescription between studies, however. Finally, the use of different pruritus and skin lesion grading instruments could have led to some imprecision in the calculation of ERs and TTEs.

Implication for research

This work highlighted the need to establish standardised outcome measures to better allow the determination of ERs and TTEs – and thus better compare – ASIT types. It is self-evident that larger clinical trials with a higher number of dogs receiving ASIT are needed, especially for the newly reported forms of SCIT that appear to provide a faster – and perhaps greater – clinical benefit than that of conventional regimens.

Author contribution

Heng Tham: Conceptualization; Data curation; Formal analysis; Methodology; Writing-original draft; Writing-review & editing. **Thierry Olivry:** Conceptualization; Supervision; Validation; Visualization; Writing-review & editing.

Supporting Information



Filename	Description
vde13048-sup-0001-TableS1.docx Word 2007 document , 28.3 KB	Table S1. Flow diagram of study selection.
vde13048-sup-0002-TableS2.docx Word 2007 document , 14.6 KB	Table S2. Data extraction from all individual studies.
vde13048-sup-0003-TableS3.docx Word 2007	Table S3. Definitions and descriptions of pruritus

Filename	Description
document , 20.7 KB	and skin lesions.
vde13048-sup-0004-AppendixS1.docx Word 2007	Appendix S1. Time-to-efficacy.
document , 59.4 KB	

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References

- 1 Hensel P, Santoro D, Favrot C, et al. Canine atopic dermatitis: detailed guidelines for diagnosis and allergen identification. *BMC Vet Res* 2015; **11**: 196.
[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 2 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.
[Wiley Online Library](#) | [CAS](#) | [Web of Science®](#) | [Google Scholar](#)
- 3 Loewenstein C, Mueller RS. A review of allergen-specific immunotherapy in human and veterinary medicine. *Vet Dermatol* 2009; **20**: 84– 98.
[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 4 Ramió-Lluch L, Brazís P, Ferrer L, et al. Allergen-specific immunotherapy in dogs with atopic dermatitis: is owner compliance the main success-limiting factor? *Vet Rec* 2020; **187**: 493.
[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 5 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.
[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 6 Münster M, Mitsch A. [Specific immunotherapy of canine atopy. A prospective clinical study using tyrosine adsorbents]. *Tierarztl Prax* 1996; **24**: 497– 504.
[PubMed](#) | [Google Scholar](#)
- 7 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 Arh* 2012; **82**: 251– 264.
[CAS](#) | [Web of Science®](#) | [Google Scholar](#)

8 Favrot C, Fischer N, Rostaher A, et al. Evaluation of plasma C-reactive protein as a biomarker in dogs with atopic dermatitis receiving allergen-specific immunotherapy: a pilot study. *Schweiz Arch Tierheilkd* 2021; **163**: 67– 72.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

9 Cucerzan A, Imre K, Morar A, et al. Effect of desensitization therapy in dogs with atopic dermatitis. *Rev Rom Med Vet* 2021; **31**: 20– 26.

[Google Scholar](#)

10 González J-L, Zalve V, Fernández-Caldas E, et al. A pilot study of immunotherapy in dogs with atopic dermatitis using a mannan-*Dermatophagoides farinae* allergoid targeting dendritic cells. *Vet Dermatol* 2018; **29**: 449-e152.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

11 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.

[Wiley Online Library](#) | [Web of Science®](#) | [Google Scholar](#)

12 Kawano K, Mizuno T. A pilot study of the effect of pullulan-conjugated Der f 2 allergen-specific immunotherapy on canine atopic dermatitis. *Vet Dermatol* 2017; **28**: 583-e141.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

13 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.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

14 Park S, Ohya F, Yamashita K, et al. Comparison of response to immunotherapy by intradermal skin test and antigen-specific IgE in canine atopy. *J Vet Med Sci* 2000; **62**: 983– 988.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

15 Park J-H, Lee W-H, Park S-J. Efficacy of half dose house dust mites-specific immunotherapy on canine atopic dermatitis. *J Vet Clin* 2017; **34**: 18– 22.

[Crossref](#) | [Google Scholar](#)

16 Willemse A, Van den Brom WE, Rijnberk A. Effect of hyposensitization on atopic dermatitis in dogs. *J Am Vet Med Assoc* 1984; **184**: 1,277– 1,280.

[CAS](#) | [Web of Science®](#) | [Google Scholar](#)

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