

Allergen-specific immunotherapy in dogs with atopic dermatitis: is owner compliance the main success-limiting factor?

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Abstract

Background While the efficacy of allergen-specific immunotherapy (ASIT) to treat canine atopic dermatitis has been well established, it remains unclear why not all dogs show the same response to treatment. The goal of the study was to determine the relationship between duration of ASIT and two measurements of success: disease severity and concomitant medication sparing effect.

Methods Data were retrospectively compiled for 145 dogs with atopic dermatitis treated with ASIT. As a measure of treatment compliance, cases were stratified into dogs treated for less than 12 months or for at least 12 months. Treatment efficacy, defined as a reduction in disease severity score (scale 0–10), was compared between both groups, and correlations between treatment success and several related factors were examined.

Results ASIT treatment duration was strongly correlated with treatment efficacy. Animals treated for less than 12 months showed lower efficacy rates (22 per cent) than those treated for at least 12 months (65 per cent). Further, in animals treated for at least 12 months, concomitant medications were reduced more (87 per cent) than in animals treated for less than 12 months (39 per cent).

Conclusion A lack of owner compliance emerged as the main factor explaining the reduced effectiveness of ASIT. To improve treatment adherence, veterinarians and owners need to be better informed about ASIT mechanisms of action before starting treatment.

Introduction

For years, allergen-specific immunotherapy (ASIT) has been used to treat dogs with atopic dermatitis (AD) and people with allergic diseases. In effect, ASIT is the only treatment able to modify the immunological response to environmental allergens and reduce clinical signs.¹ The safety of ASIT for people and dogs has also been well established.^{2–3} However, in people, despite its proven effectiveness in the management of asthma and allergic

rhinitis, this good response has not been as clear in patients with AD.^{4–5}

In dogs, controlled studies examining the efficacy of ASIT have been limited.³ The main reasons for this are the long time required to assess treatment efficacy and the high rates of treatment discontinuation.^{3–6–8} Some retrospective and non-controlled studies have suggested that ASIT is effective in controlling the clinical signs of AD in 50–80 per cent of treated dogs.^{9–14} However, it is still difficult to understand how and why some dogs show an excellent response to ASIT, whereas others show little or no improvement after months of treatment.

The present retrospective study was therefore designed to determine the relationship between the duration and the efficacy of ASIT to treat atopic dogs.

Materials and methods

Animals

Clinics were chosen from Laboratorios LETI database by selecting those that had at least two animals starting ASIT treatment from the beginning of 2016 to the end

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of 2017. The study monitor asked clinics to participate and 16 accepted. Information about procedure confidentiality was provided to all clinicians. An informed consent was obtained from each participant, and all data obtained from clinical reports were treated following data protection rules stated by the Spanish law LOPDGDD 3/18.

After examining the clinical records of 145 dogs with AD treated with ASIT, all patients aged ≥ 12 months were selected according to the following criteria: (1) diagnosis of AD (compatible clinical signs in the absence of flea infestation or food hypersensitivity), (2) an available and complete clinical record, and (3) treatment started at least one year before enrolment. To

include an animal in the study, it was mandatory to fit the three inclusion criteria.

Treatment

Participating dogs were prescribed subcutaneous ASIT treatment (Letivet Retard, Laboratorios LETI, Spain). Allergens were identified in each dog by an in vitro allergen-specific IgE test (Greer ELISA, Lenoir, USA). All selected dogs had hypersensitivity to mites and/or pollens.

Questionnaire

Veterinary dermatologists at each clinic completed a 13-question survey (figure 1) using their patient

1- Dates of the first ASIT and last ASIT:
2- On the scale below, please rate the severity of your patient's allergy when it came to your clinic.
3- On the scale below, please rate the severity of your patient's allergy after ASIT treatment.
4- How satisfied are you with ASIT treatment? ☐ ☐ ☐ ☐ ☐ Very satisfied Satisfied Indifferent Unsatisfied Very unsatisfied
5- If satisfied, when did you observe an improvement in clinical sign(s)?
6- Please indicate the medication the patient was on before ASIT treatment (compound/s and dose/s):
7- Did the patient need medication after ASIT treatment? - NO - YES: MORE / SAME/ LESS medication than before ASIT. Please indicate product/s and dose/s):
8- If your patient is NOT currently on medication, please choose the reason that best fits: - The problem resolved - The problem was mild so no medication was needed - No medication helped so I stopped prescribing any - Dog resists taking oral medication
9- Is your patient still receiving ASIT injections? - NO - YES
10- If your patient is no longer receiving ASIT injections, please indicate why from the list below: - Treatment was not effective - The owner and dog did not return to the clinic - The dog did not tolerate the injections - Allergy signs disappeared - The owner could not afford treatment - Don't know
11- Were there adverse reactions to ASIT at any time? - NO - YES: describe these reactions and when they occurred (date and time-relation to ASIT):
12- What allergy-related problem(s) does the patient still have that require(s) veterinary visits? (mark those that apply) None / Ear infection / Hair loss / Itchy skin / Odour / Skin infection Other: _____
13- How often is the patient bathed? Once a week / Twice a month / Once a month / Less than once a month

Figure 1 Questionnaire completed by the veterinarians responsible for each participant. ASIT, allergen-specific immunotherapy.

records. Complete clinical records need to provide all the information needed to answer each question, otherwise the animal was not eligible. Questions were designed to provide information on medical history and physiological and pathological characteristics of each animal. The questionnaire included a visual analogue scale ranging from 0 to 10 for the subjective assessment of the severity of clinical signs both before and after the treatment. In addition, veterinarians were asked about any topical or systemic medication the dogs were receiving before, during and after ASIT treatment.

Efficacy assessment criteria

Efficacy levels of ASIT were described according to the criteria of Zur *et al.*¹¹ These levels take into consideration reduction in the severity of clinical signs and reduction in concurrent medication.

Statistical analysis

Efficacy analysis was performed considering two groups: (1) dogs that had received ASIT for a period of time shorter than 12 months and (2) dogs that had received ASIT for at least 12 months. The rationale for this division was that 12 months is considered the minimal time required to properly evaluate the response to ASIT for AD in dogs.³

A Student's paired *t* test was used to compare the mean atopy severity scores before and after treatment. Additionally, differences in score pre-post treatment were calculated for both groups and compared with a Student's *t* test for independent samples. Drug sparing effects were compared before and after treatment using a chi-squared or likelihood ratio test. The analysis was performed with SAS V.9.4 software (SAS Institute, Cary, North Carolina, USA). The significance level was set at $P < 0.05$.

Results

Animals

Of the 145 dogs, 73 were male (50 per cent) and 72 were female (50 per cent). The mean age was 6 ± 2 years. Most of the dogs (73 per cent) had presented with their first clinical signs of AD before the age of

two years. Participants were of 48 different breeds: the most common were mixed breed dogs ($n=20$), Labrador retriever ($n=16$), French bulldog ($n=15$), Yorkshire terrier ($n=7$), German shepherd dog ($n=6$), shih tzu ($n=5$) and dachshund ($n=5$). No correlation between sex, breed or age of onset and ASIT efficacy was observed.

ASIT composition

ASIT was prepared as an individual formulation based on the allergen sensitisation profile of each patient. Eighty-one animals (56 per cent) were treated with only mite extracts, 50 (34 per cent) with a mixture of pollens and mites, and only 14 (10 per cent) of the ASIT were formulated exclusively with pollens. No correlation was found between treatment efficacy and the number or type of allergens.

Treatment duration

Of the 145 animals included, 36 (25 per cent) discontinued treatment before 12 months and 109 continued with the treatment regimen beyond 12 months. Results indicate that among the animals treated for at least 12 months, significantly higher rates of clinical improvement ($P < 0.001$) were recorded (figure 2). Hence, eight animals (22 per cent) treated for under 12 months showed an improvement of more than 50 per cent in clinical signs, while in the group of animals treated for at least 12 months this rate was 65 per cent ($n=71$).

After ASIT treatment, the mean disease severity scores (0–10 scale) significantly decreased ($P < 0.001$) in both the animals treated for less than 12 months and those treated at least 12 months (figure 3). The difference recorded in this score was, nevertheless, greater in the longer treated animals: 7.7 ± 1.2 (mean $\pm$ sd) pretreatment and 3.4 ± 2.3 post-treatment in the ≥ 12 months group and 8.0 ± 1.4 and 6.0 ± 1.9 , respectively, in the < 12 months treatment group.

The mean time elapsed before the onset of improvement in clinical signs was 5 ± 2 months.

Concomitant medication sparing effect

The drugs most frequently reported as concomitant medication were anti-inflammatory and

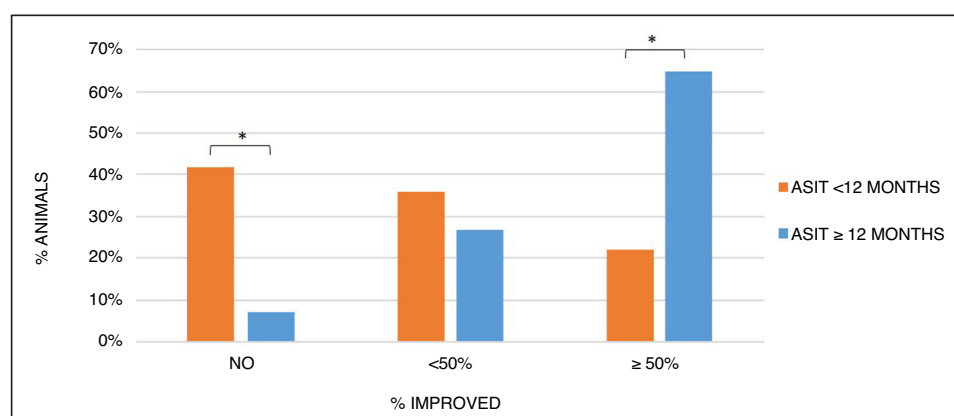


Figure 2 Percentage improvement in clinical signs after allergen-specific immunotherapy (ASIT) treatment in dogs treated for under 12 months ($n=36$) or at least one year ($n=109$). Significant differences were detected between groups ($*P < 0.001$).

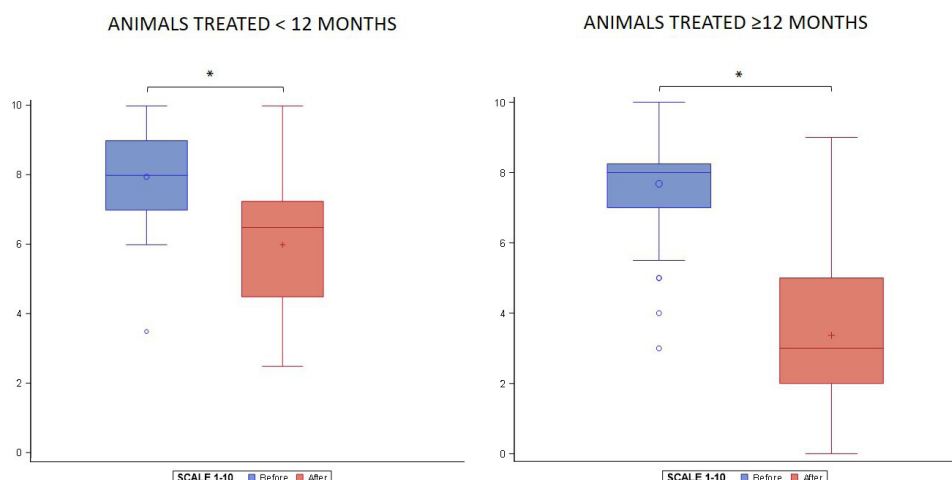


Figure 3 Disease severity scores according to treatment duration. Significant differences were found in clinical signs before and after allergen-specific immunotherapy treatment in both groups (* $P<0.001$).

immunomodulatory agents (oclacitinib, glucocorticoids, cyclosporine), antibiotics, antifungals and antiseptics.

Significant differences were observed between the two treatment duration groups in concomitant medication sparing. Thus, in 87 per cent of animals in the ≥ 12 months treatment group, concomitant medication was reduced or withdrawn after ASIT treatment, while in the < 12 months treatment group this percentage was significantly lower (39 per cent) ($P<0.001$).

When the numbers of dogs receiving each type of medication before and after 12 months of ASIT were compared, differences were significant ($P<0.05$) for almost all drugs (figure 4).

Safety

No serious side effects were described in any of the animals included in this study. Four animals showed a mild reaction. The main adverse effects observed were vomiting, apathy and transient mild inflammation at the injection site. In no dog was treatment discontinued due to adverse reactions.

Discussion

In this retrospective study, the authors assessed through a 13-question survey the main possible causes of the limited success of ASIT in controlling clinical signs of AD in 145 dogs.

The results revealed no impact on the effectiveness of ASIT treatment of physiological factors such as dog breed, sex or age, as described by other authors.^{11 12 15} If other aspects more related to the disease or treatment such as ASIT components (mites, pollens or both), number of allergens or onset of AD are considered, again no correlation was found between these and ASIT response, in line with the data available in the literature.^{11 12 16}

In contrast, a determining effect was detected of ASIT treatment duration. This meant that treatment was more effective in animals that had been treated for at least 12 months, as recommended by the International Committee on Allergic Diseases of Animals,³ in that 65 per cent showed an improvement in clinical signs of

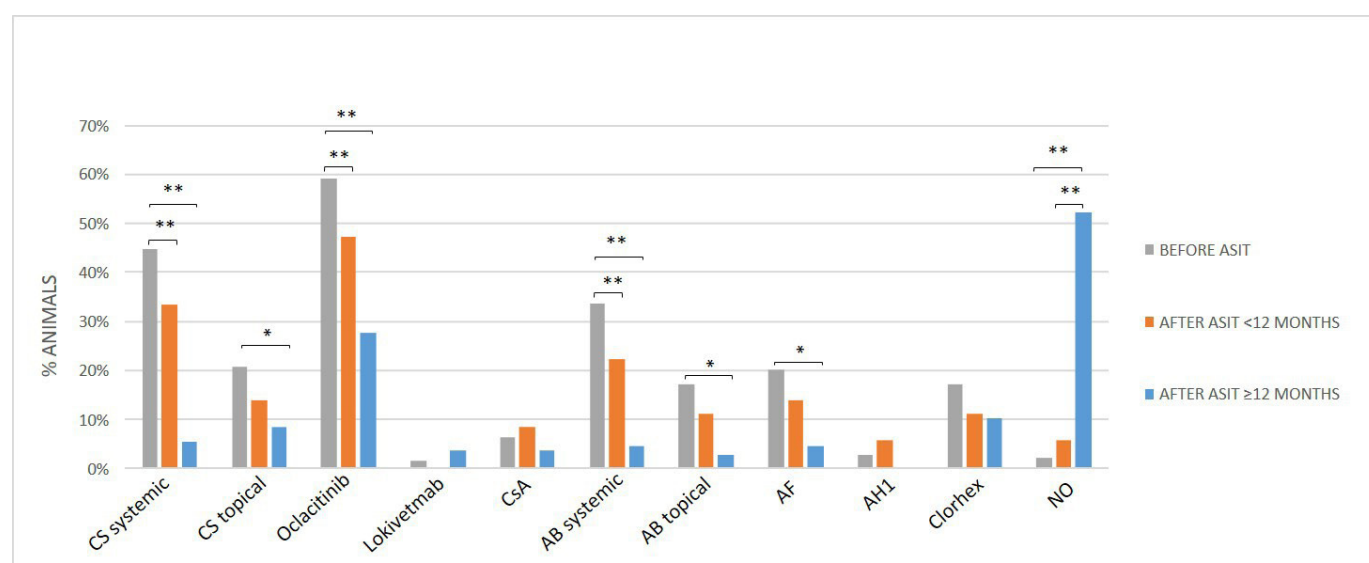


Figure 4 Drug sparing effect of allergen-specific immunotherapy (ASIT) treatment. Topical and systemic medications administered to the atopic dogs before and after ASIT treatment. Dogs treated for at least 12 months showed more significant reductions in concomitant medications than those treated for less than 12 months (* $P<0.05$, ** $P<0.001$). AB, antibiotics; AF, antifungals; AH1, antihistaminics; clorhex, chlorhexidine; CS, corticosteroids; CsA, cyclosporine; NO, no medication.

more than 50 per cent versus only 22 per cent in the other group. These longer-treated animals also showed a medication sparing effect in response to treatment.

Owner compliance is currently an important challenge in ASIT treatment. Several studies have shown that a large percentage of clients failed to continue with ASIT for more than 12 months.^{9 17} In effect, the withdrawal rate for immunotherapy is higher than that reported for any other pharmacological treatment.¹⁸ This can be easily explained by the long duration and demanding nature of treatment and also that signs of improvement are not appreciable until after several months of treatment.

In contrast, one of the stronger points of this treatment is its safety.¹³ In agreement, no serious side effects in any of the treated patients were observed.

Retrospective studies such as this one allow for assessment of real-life treatments without the pressure often exerted by the veterinarian on dog owners in prospective studies.^{17 19–22} However, retrospective studies have limitations, including the impossibility of using validated scores to grade disease severity, such as canine atopic dermatitis extent and severity index (CADESI).²³ In the present study, a number of different clinicians managed different cases and each one provided severity index scores (on a scale of 0–10) from their medical records. The use of such records rather than the veterinarian's opinion confers some degree of objectivity, but different subjective criteria among clinicians should be taken in consideration. The present study therefore has several limitations, including those mentioned above; in some cases the records did not contain detailed information on the reasons for treatment cessation, or different possible reasons were described, as noted in other retrospective studies.^{24 25}

Other biases in the information recruitment need to be addressed. Because clinics were selected among those where ASIT is frequently prescribed, a bias in the selection process should be taken into account. On the contrary, the animal selection bias was minimum, since when the veterinarian accepted the participation in the study all cases that fit the inclusion criteria were included in the study. Moreover, survey biases could be considered, since treatment outcomes are self-reported and veterinarians may have rated their patients better than they actually did, overestimating the response rate of ASIT. Even though the response rate of ASIT treatment could be overestimated, the study of concurrent medication would be a factor that will allow a more objective efficacy measurement.

Collectively, the results of the present study reveal better treatment outcomes for canine AD with longer durations of ASIT. As the host immune response is the mechanism of action of ASIT, a long period is required for a dog with AD to mount an effective response. Veterinarians need to help their clients understand

the importance of completing the prescribed length of treatment to improve compliance and therefore ASIT efficacy.^{10 26}

A rapid improvement is also important for owner compliance. In the case of AD this determines a need for several concurrent therapies in early disease stages to rapidly reduce clinical signs and make adherence to ASIT easier. In this study, it was confirmed that 87 per cent of the animals treated for 12 months had a considerable drug sparing effect, and in 52 per cent of the cases no concurrent medication was needed after 12 months of ASIT treatment.

In view of the present results, it could be argued that low efficacy is not a consequence of lack of compliance, but the opposite: the low compliance is due to the fact that the expected results were not achieved. In other words, the owners interrupted the treatment because the patients did not improve. However, it should be noted that in many cases the improvement begins after nine months or more of ASIT, and therefore it is essential, as indicated in the literature,³ to continue the treatment for at least one year. The data show that in cases where the recommended time was allowed, the success rate increased to 65 per cent. The recommendation is that veterinarians should be well informed so that they can instruct their clients and perhaps also select those that are more likely to show good compliance with ASIT and therefore a better response of their pets to treatment.

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Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Data are stored in Laboratorios LETI and are available from the corresponding author.

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