

Update on Allergen Immunotherapy

Ralf S. Mueller, DMV

KEYWORDS

- Allergen specific • Desensitization • Hyposensitization • Feline • Canine
- Intralymphatic

KEY POINTS

- Allergen immunotherapy is the only specific therapy for atopic dermatitis in dogs and cats.
- Selection of allergens should be based on clinical history of the animal in conjunction with positive reactions on intradermal or serum testing.
- To optimize success, the protocol should be individualized to each patient; when adapting the dose and/or frequency during the treatment, most animals show a good to excellent response.
- Adverse effects include increased pruritus and very rarely anaphylactic reactions.
- Subcutaneous, intralymphatic, and oro-mucosal administration routes have been reported; the subcutaneous route is most frequently used.

INTRODUCTION

Allergen immunotherapy (AIT) is the only treatment of atopic dermatitis that is able to change the pathogenic mechanisms of the disease. By injecting relevant allergens, AIT aims at initiating an immune response that leads to activation of regulatory T cells and immunosuppressive cytokines with a subsequent improvement of clinical signs. In the past, the term *allergen-specific immunotherapy* was used; but as AIT by definition contains specific allergens, AIT is as accurate and avoids stating the obvious. AIT has been used successfully in several animal species but is most commonly used in dogs. Data in cats are more limited. Initially, AIT was administered subcutaneously; but intralymphatic and sublingual or oral immunotherapy protocols have also been described.

Disclosure Statement: In the last 5 years, R.S. Mueller has received support from Artu Biologics and Heska Corporation for studies evaluating immunotherapy and serum testing for identification of allergens involved in canine atopic dermatitis, respectively.

Centre for Clinical Veterinary Medicine, Medizinische Kleintierklinik, LMU Munich, Veterinaerstr. 13, Munich 80539, Bavaria, Germany

E-mail address: R.Mueller@lmu.de

Vet Clin Small Anim ■ (2018) ■–■

<https://doi.org/10.1016/j.cvsm.2018.08.001>

0195-5616/18/© 2018 Elsevier Inc. All rights reserved.

vetsmall.theclinics.com

SELECTION OF ALLERGENS FOR ALLERGEN IMMUNOTHERAPY

For many years, intradermal testing was the gold standard for the identification of offending allergens in animals with atopic dermatitis. Today serum tests for allergen-specific immunoglobulin E (IgE) are also used, and the success rate of AIT seems to be the same when allergens are chosen based on skin testing compared with serum testing.¹ Interassay and intraassay variability of serum testing has been evaluated in several studies, some of which showed a high reproducibility²; in others the reproducibility was much lower,³ emphasizing the need for independent evaluation of a testing method before it can be recommended. As healthy dogs show numerous positive reactions on both skin and serum tests,^{4,5} allergens should be chosen not only based on test results but also on clinical history. For example, if in a temperate climate an atopic dog shows severe pruritus all year round yet only has a strong reaction to birch pollen, this would not explain its clinical signs. Similarly, in a dog that exhibits clinical signs only in spring or summer and shows a strong positive reaction to house dust mites, it is unlikely the clinical signs are due to dust mites. Positive skin test or serum test results indicate sensitization against an allergen with subsequent IgE production, not necessarily clinically relevant hypersensitivity. Consequently, skin or serum test results are not suitable to make a diagnosis of environmental allergies in any species because of those false-positive reactions and should only be used with the aim to identify allergens suitable for AIT in animals that are diagnosed with atopic dermatitis based on history, clinical examination, and having ruled out differential diagnoses. Thus, pros and cons of AIT need to be discussed with the owners and AIT chosen as desired therapy before performing those tests. Subsequently, the results of either intradermal testing or testing for allergen-specific IgE should be interpreted in light of the clinical history of that particular patient; the allergens included in the treatment solution should be chosen based on this history.

MECHANISM OF ACTION

Most available information about the mechanism of action of AIT derives from studies with dogs and parallels what is seen in humans (**Box 1**). An increase in so-called blocking IgG antibodies was described in dogs undergoing immunotherapy^{6,7}; but an actual binding and, thus, inactivation of offending allergens by those antibodies have not been demonstrated as of yet; it is not known whether production of those allergen-specific antibodies during AIT is correlated to a good clinical response. An increase in FoxP3+ regulatory T cells and IL-10 and a decrease in allergen-specific IgE have been associated with successful immunotherapy in one study.⁸ In cats with experimental asthma that underwent rush immunotherapy (RIT) with CpG

Box 1

Mechanisms of action of allergen immunotherapy in dogs and humans

- IgG4 ↑
- FoxP3+ CD4+ Treg ↑
- IL-10 ↑
- IL-4 ↓
- IgE ↓

Abbreviations: IgG4, immunoglobulin G4; IL, interleukin; Treg, regulatory T cell.

oligodeoxynucleotides, the percentage of eosinophils in the bronchoalveolar lavage fluid (BALF) decreased significantly with immunotherapy; but the number of regulatory T cells in the peripheral blood and the concentration of IL-10 or interferon-gamma in the BALF did not change.⁹

SUBCUTANEOUS ALLERGEN IMMUNOTHERAPY

Traditionally, allergens in AIT of canine atopic dermatitis (as in other species) are injected subcutaneously during the induction period in gradually increasing volume and concentration over a few weeks to a few months depending on the protocol.¹⁰ Thereafter maintenance therapy is administered with the same amount of allergen extract every few weeks to once monthly for a period of several years. However, most dermatologists agree that the amount of allergen and the frequency of injections have to be adjusted to individual patients. If a dog shows increased pruritus directly after the injection, that then subsides again a few days later, the dose should be reduced at the next injection. If the pruritus improves after the injections but then increases again some time before the next allergen administration, a shorter interval between injections is advisable. The final response should not be evaluated until 12 months after beginning AIT. Owners need to be made aware before choosing immunotherapy that it may take 1 year until maximal improvement has been achieved.

Patients on immunotherapy may need additional antipruritic medication during the first months of treatment. Essential fatty acids, antihistamines, lokivetmab, and shampoo therapy are unlikely to interfere with tolerance induction. However, the author prefers not to use glucocorticoids, cyclosporine, and oclacitinib as long-term therapy during the first year of AIT but rather as short treatment courses as needed.

Many studies evaluating subcutaneous AIT (SCIT) show an excellent response or a good improvement in approximately two-thirds of the dogs, independent of age, sex, breed, type of allergen, perennial or seasonal clinical signs, and high- or low-dose protocols (Table 1).¹ The few studies evaluating RIT, oro-mucosal immunotherapy (OIT), and intralymphatic immunotherapy (ILIT) reported similar success rates.^{11–13} However, most studies included a small number of dogs and were case studies¹; only a few studies were randomized and double blinded.^{12,14,15} Thus, the results need to be interpreted with caution; more studies are needed to determine factors optimizing treatment outcomes. In addition, dose-finding studies were performed only, rarely, in dogs; their results have not been conclusive.^{1,15,16}

Table 1
Success rate of canine allergen immunotherapy in various studies

Study Reference	Success Rate (% Good to Excellent Responders)	Number of Dogs Included
Keppel et al, ⁸ 2008	51	53
Mueller & Bettenay, ¹⁷ 1996	58	146
Nuttall et al, ¹⁸ 1998	22 ^a	186
Schnabl et al, ¹⁶ 2006	64	117
Scott et al, ¹⁹ 1993	60	144
Zur et al, ²⁰ 2002	52	169

^a Most studies evaluated responses as excellent, good, mild/moderate, and poor; this particular study only graded responses as good, partial, or none; 22% showed a good and 39% a partial response.

RUSH IMMUNOTHERAPY

With subcutaneous RIT, the induction period of several weeks to months is abbreviated to 1 day and injections are given hourly. Dogs are continuously monitored clinically in a hospital setting. In human medicine, RIT is performed to achieve a more rapid improvement, particularly in patients with venom hypersensitivities, but is associated with a high rate of anaphylactoid reactions. In dogs, RIT is well tolerated and has mainly been associated with increased pruritus; more severe reactions have been extremely rare.^{12,21} The protocol in dogs includes a recommendation of an antihistamine administration 1 or 2 hours before the injection of the allergen extract. In a double-blinded study, the maximum improvement in clinical signs was reached after 6.8 months with RIT compared with 9.2 months with classic immunotherapy; however, in this study the difference failed to reach statistical significance.¹² RIT with alum-precipitated allergens has been reported with similar safety and success rates as RIT with aqueous allergens.²² RIT has also been reported in 4 cats,²³ but this number is too small to make any conclusions about safety; efficacy was not reported in this case series.

ORO-MUCOSAL IMMUNOTHERAPY

Oral immunotherapy has been available in some countries for several years. In humans with sublingual immunotherapy (SLIT), small amounts of allergens are administered and kept under the tongue for several minutes without swallowing; in oral immunotherapy, allergens are swallowed after oral administration. In dogs, a small amount of extract is applied between the lips and gums once to twice daily. Consequently, in animals, OIT is probably the better term. Improvement of clinical signs and a decrease in allergen-specific IgE were reported in a small number of dogs with this type of AIT.¹³ A larger clinical study a few years ago showed a reasonable success rate comparable with that seen with SCIT.²⁴ In addition, dogs improved on OIT that had previously failed to improve on SCIT. Unfortunately, this study is not published. Further scientific studies are needed to evaluate optimal treatment protocols for this treatment option.

INTRALYMPHATIC IMMUNOTHERAPY

In humans, ILIT is associated with a prolonged improvement after 3 monthly injections and was reported to be safer and better tolerated than SCIT.^{25,26} In dogs, several studies have evaluated ILIT and reported it a safe treatment alternative to SCIT or OIT.^{11,27,28} A smaller amount of allergen extract (typically 0.1 mL) is injected in the submandibular or popliteal lymph node monthly. Based on published data, prolonged improvement is only seen in a small number of dogs; most patients will need continuous intralymphatic or subcutaneous injections, especially when aqueous allergens are used.²⁷ The author has seen some dogs improve on ILIT that previously failed to improve on SCIT. Short- and mid-term adverse effects seem to be very rare.^{11,27,28} Long-term adverse effects of ILIT are not known, and further studies about long-term safety are particularly needed with alum-precipitated extracts.

FELINE ALLERGEN IMMUNOTHERAPY

Atopic dermatitis in cats is not well defined. There is evidence for causal involvement of allergens in cats with noninflammatory alopecia, severe head and neck pruritus, lesions of the eosinophilic granuloma complex, miliary dermatitis, and feline asthma.^{9,29} In cats with skin disease, few studies are published evaluating AIT; almost all of them

evaluated SCIT in a small number of cats.^{1,29–31} All of those studies showed success rates similar to what is seen in dogs with atopic dermatitis. One study reported successful RIT in 4 cats.²³ No studies have been published evaluating ILIT or SLIT in cats. More information is published about the treatment of cats with asthma sensitized to various allergens in a laboratory setting.³² Successful RIT with a decrease in eosinophil numbers in bronchoalveolar lavage has been reported even when the allergen used in the extract was either not the allergen the cats were sensitized to or not the only allergen the cats were sensitized to.³³ When bacterial oligodeoxynucleotides were used as an adjuvant to RIT in those cats with experimental asthma, eosinophilic airway inflammation was also significantly alleviated.⁹

ADVERSE EFFECTS OF IMMUNOTHERAPY

Increased pruritus after allergen administration is the most common adverse effect seen with subcutaneous immunotherapy.¹ In many cases, this can be alleviated by decreasing the volume of allergen extract injected. Other animals may benefit from the administration of an antihistamine 2 hours before allergen injection. In some cases, this may be due to adjuvants; in a double-blinded study 3 of 27 dogs treated with alum-precipitate allergens and 2 of 24 dogs treated with an alum-containing placebo showed generalized pruritus.¹⁴ Localized injection reactions may rarely be seen.¹ In a small number of patients (<1%), systemic reactions may occur and include anxiety, depression, diarrhea, hyperactivity, sleepiness, urticaria/angioedema, vomiting, weakness, and very rarely collapse and anaphylaxis.¹ For milder adverse effects, glucocorticoids or antihistamines may be administered; however, in patients with anaphylaxis, intravenous epinephrine is the treatment of choice.

SUMMARY

AIT is a good treatment option for environmental allergy in dogs and cats. It is the only specific therapy and the only treatment reported to change the patho-mechanisms of the disease. Subcutaneous immunotherapy combines a satisfactory success rate with a good safety profile. Anaphylactic reactions are rarely seen in animals. In addition to the subcutaneous administration of allergens, more recent routes of administration, such as intralymphatic and OIT, have been described. Pilot studies with different adjuvants, such as bacterial oligodeoxynucleotides,^{9,34,35} pullulan,³⁶ or mannan,³⁷ have been published; their use may further increase safety and efficacy. The first trials have reported the use of recombinant allergens.³⁸ However, as most of the published studies are case series with often rather small numbers of animals included, more and larger randomized studies of immunotherapy are needed in a clinical setting to provide guidance on the optimal selection of allergens, adjuvants, dosing, success rate, and adverse effects of the various protocols of immunotherapy in dogs and cats.

REFERENCES

1. Loewenstein C, Mueller RS. A review of allergen-specific immunotherapy in human and veterinary medicine. *Vet Dermatol* 2009;20:84–98.
2. Thom N, Favrot C, Failing K, et al. Intra- and interlaboratory variability of allergen-specific IgE levels in atopic dogs in three different laboratories using the Fc-epsilon receptor testing. *Vet Immunol Immunopathol* 2010;133:183–9.
3. Patterson AP, Schaeffer DJ, Campbell KL. Reproducibility of a commercial in vitro allergen-specific assay for immunoglobulin E in dogs. *Vet Rec* 2005;157:81–5.

4. Mueller RS, Fieseler KV, Rosychuk RA, et al. Intradermal testing with the storage mite *Tyrophagus putrescentiae* in normal dogs and dogs with atopic dermatitis in Colorado. *Vet Dermatol* 2005;16:27–31.
5. Lian TM, Halliwell RE. Allergen-specific IgE and IgGd antibodies in atopic and normal dogs. *Vet Immunol Immunopathol* 1998;66:203–23.
6. Hou CC, Griffin CE, Hill PB. Dermatophagoides farinae-specific IgG responses in atopic dogs undergoing allergen-specific immunotherapy with aqueous vaccines. *Vet Dermatol* 2008;19:215–20.
7. Hites MJ, Kleinbeck ML, Loker JL, et al. Effect of immunotherapy on the serum concentrations of allergen-specific IgG antibodies in dog sera. *Vet Immunol Immunopathol* 1989;22:39–51.
8. Keppel KE, Campbell KL, Zuckermann FA, et al. Quantitation of canine regulatory T cell populations, serum interleukin-10 and allergen-specific IgE concentrations in healthy control dogs and canine atopic dermatitis patients receiving allergen-specific immunotherapy. *Vet Immunol Immunopathol* 2008;123:337–44.
9. Reiner CR, Cohn LA, Delgado C, et al. Adjuvanted rush immunotherapy using CpG oligodeoxynucleotides in experimental feline allergic asthma. *Vet Immunol Immunopathol* 2008;121:241–50.
10. Griffin CE, Hillier A. The ACVD task force on canine atopic dermatitis (XXIV): allergen-specific immunotherapy. *Vet Immunol Immunopathol* 2001;81:363–83.
11. Timm K, Mueller RS, Nett-Mettler CS. Long term effects of intralymphatic immunotherapy (ILIT) in canine atopic dermatitis. *Vet Dermatol* 2018;29:123–30.
12. Mueller RS, Fieseler KV, Zabel S, et al. Conventional and rush immunotherapy in canine atopic dermatitis. In: Hillier A, Foster AP, Kwochka KW, editors. *Advances in veterinary dermatology V*. Oxford (England): Blackwell Publishing; 2005. p. 60–9.
13. DeBoer DJ, Verbrugge M, Morris M. Clinical and immunological responses of dust mite sensitive, atopic dogs to treatment with sublingual immunotherapy (SLIT). *Vet Dermatol* 2016;27:82–87e23.
14. Willemse A, Van den Brom WE, Rijnberk A. Effect of hyposensitization on atopic dermatitis in dogs. *J Am Vet Med Assoc* 1984;184:1277–80.
15. 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;16:162–70.
16. Schnabl B, Bettenay SV, Dow K, et al. Results of allergen-specific immunotherapy in 117 dogs with atopic dermatitis. *Vet Rec* 2006;158:81–5.
17. Mueller RS, Bettenay SV. Long-term immunotherapy of 146 dogs with atopic dermatitis - a retrospective study. *Aust Vet Pract* 1996;26:128.
18. Nuttall TJ, Thoday KL, van den Broek AH, et al. Retrospective survey of allergen immunotherapy in canine atopy. *Vet Rec* 1998;143:139–42.
19. Scott KV, White SD, Rosychuk RAW. A retrospective study of hyposensitization in atopic dogs in a flea scarce environment. In: Ihrke PJ, Mason IS, White SD, editors. *Advances in veterinary dermatology*. Oxford (England): Pergamon Press; 1993. p. 79–87.
20. Zur G, White SD, Ihrke PJ, et al. Canine atopic dermatitis: a retrospective study of 169 cases examined at the University of California, Davis, 1992-1998. Part II. Response to hyposensitization. *Vet Dermatol* 2002;13:103–11.
21. Mueller RS, Bettenay SV. Evaluation of the safety of an abbreviated course of injections of allergen extracts (rush immunotherapy) for the treatment of dogs with atopic dermatitis. *Am J Vet Res* 2001;62:307–10.

22. Hobi S, Mueller RS. Efficacy and safety of rush immunotherapy with alum-precipitated allergens in canine atopic dermatitis. *Tierarztl Prax Ausg K Kleintiere Heimtiere* 2014;42:167–73.
23. Trimmer AM, Griffin CE, Boord MJ, et al. Rush allergen specific immunotherapy protocol in feline atopic dermatitis: a pilot study of four cats. *Vet Dermatol* 2005;16:324–9.
24. DeBoer D, Morris M. Multicentre open trial demonstrates efficacy of sublingual immunotherapy in canine atopic dermatitis (abstract). *Vet Dermatol* 2012;23:65.
25. Senti G, Crameri R, Kuster D, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. *J Allergy Clin Immunol* 2012;129:1290–6.
26. Hylander T, Larsson O, Petersson-Westin U, et al. Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. *Respir Res* 2016;17:10.
27. Hatzmann K, Mueller RS. Practicability and safety of intralymphatic allergen-specific immunotherapy in dogs with atopic dermatitis. *Annual Congress of the European Society of Veterinary Dermatology*. Bruxelles: Veterinary Dermatology, 2011;463–4.
28. Fischer N, Rostaher A, Favrot C. Intralymphatic immunotherapy: an effective and safe alternative route for canine atopic dermatitis. *Schweiz Arch Tierheilkd* 2016;158:646–52.
29. Ravens PA, Xu BJ, Vogelnest LJ. Feline atopic dermatitis: a retrospective study of 45 cases (2001-2012). *Vet Dermatol* 2014;25:95–102.
30. Prost C. Atopy in the cat: 28 cases. *Proceedings of the Second World Congress of Veterinary Dermatology*, Montreal, Canada, 1992; p. 87.
31. Bettenay SV. Response to hyposensitization in 29 atopic cats. In: Kwochka KW, Willemse A, von Tscharner C, editors. *Advances in veterinary dermatology*. Oxford (England): Butterworth/Heinemann; 1998. p. 517–8.
32. Norris Reinero CR, Decile KC, Berghaus RD, et al. An experimental model of allergic asthma in cats sensitized to house dust mite or bermuda grass allergen. *Int Arch Allergy Immunol* 2004;135:117–31.
33. Reinero C, Lee-Fowler T, Chang CH, et al. Beneficial cross-protection of allergen-specific immunotherapy on airway eosinophilia using unrelated or a partial repertoire of allergen(s) implicated in experimental feline asthma. *Vet J* 2012;192:412–6.
34. Rostaher A, Fuchs S, Weber K, et al. Immunomodulatory effects of CPG oligodeoxynucleotides delivered by gelatine nanoparticles in the treatment of canine atopic dermatitis – a pilot study. *Vet Dermatol* 2013;24:494–500.
35. Mueller RS, Veir J, Fieseler KV, et al. Use of immunostimulatory liposome-nucleic acid complexes in allergen-specific immunotherapy of dogs with refractory atopic dermatitis - a pilot study. *Vet Dermatol* 2005;16:61–8.
36. 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.
37. Soria I, Alvarez J, Manzano AI, et al. Mite allergoids coupled to nonoxidized mannan from *Saccharomyces cerevisiae* efficiently target canine dendritic cells for novel allergy immunotherapy in veterinary medicine. *Vet Immunol Immunopathol* 2017;190:65–72.
38. Olivry T, Paps JS, Dunston SM. Proof of concept of the preventive efficacy of high-dose recombinant mono-allergen immunotherapy in atopic dogs sensitized to the *Dermatophagoides farinae* allergen Der f 2. *Vet Dermatol* 2017;28:183-e140.