



Allergen Specific Immunotherapy in Canine Atopic Dermatitis: an Update

Nina M. Fischer¹ · Ralf S. Müller²

Published online: 21 November 2019

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Abstract

Purpose of Review This review aims to evaluate new insights into allergen immunotherapy (AIT) and review the mechanism, different protocols used, and response rate of this treatment option for canine atopic dermatitis.

Recent Findings AIT is the only etiological treatment available for canine atopic dermatitis. Selection of allergens is based on clinical history in conjunction with positive reactions on intradermal and serum testing. During decades AIT was applied subcutaneously (SCIT) using aqueous or aluminum-precipitated solution of allergens, but in the last few years, new routes like sublingual (SLIT), intralymphatic (ILIT), and epicutaneous administration are on the rise. AIT combines a satisfactory success rate (around 70%) with a good safety profile. Adverse effects include mainly increased pruritus and anaphylactic reactions are rarely seen in animals. Pilot studies with different adjuvants to further increase safety and efficacy have been published.

Summary AIT is a safe and effective therapy for canine atopic dermatitis. 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.

Keywords Allergen specific · Desensitization · Hyposensitization · Feline · Canine · Intralymphatic

Introduction

Canine atopic dermatitis (CAD) is a pruritic and inflammatory skin disease in genetically predisposed dogs, which is often associated with high serum IgE concentrations against environmental allergens [1–3].

Allergen (-specific) immunotherapy (AIT) is the sole etiological treatment of CAD [4, 5]. After injections of relevant allergens, the allergic patient's immune response should be modulated to activate regulatory T cells and initiate the pro-

duction of IL-10 as well as blocking IgG antibodies [6]. If a positive response to AIT is seen within the first 12 months, this immunomodulation is administered long term and sometimes lifelong [7••].

The efficacy of AIT as a treatment of CAD has been assessed in two randomized controlled trials and several open studies and ranged from 50 to 70%, depending on the protocol designs and outcome measures used [5, 8–10]. Moreover, multiple controlled studies have demonstrated the efficacy of AIT in the management of allergic disorders in humans although there are still controversies about its efficacy for atopic dermatitis [11•, 12].

Relevant allergens are usually determined based on history in association with intradermal tests and/or in vitro allergy testing [4, 5]. During decades, AIT was applied subcutaneously (SCIT) using aqueous or aluminum-precipitated solution of allergens [7••, 13]. In the last few years, sublingual (SLIT) [14, 15], intralymphatic (ILIT) [16, 17•], and epicutaneous [18] administration of allergens have been advocated. Furthermore, as in human medicine, recombinant allergens have been used instead of crude allergen solutions [19••, 20•, 21•].

This article is part of the Topical Collection on *Veterinary Dermatology*

✉ Nina M. Fischer
nfischer@vetclinics.uzh.ch

¹ Dermatology Unit, Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Winterthurerstrasse 260, 8057 Zurich, Switzerland

² Zentrum für klinische Tiermedizin, LMU Munich, Veterinaerstrasse 13, 80539 Munich, Germany

This review aims to evaluate new insights into AIT and review the mechanism, different protocols used, and response rate of this treatment option for canine atopic dermatitis.

Mechanism of Action

In human medicine, the induction of regulatory T (Treg) cells seems to be mainly responsible for clinical improvement [22, 23]. Treg cells produce a variety of cytokines and especially IL-10 and TGF- β seem to play a key role in AIT by suppressing Th2-type immune responses. Consequently, mast cells, basophils, and eosinophils are downregulated and the production of pro-inflammatory cytokines is inhibited. Furthermore, IL-10 and TGF- β induce blocking IgG4 antibodies and decrease B cell antigen-specific IgE production [11, 23–25].

Thus, lymphoproliferative responses to allergens are reduced after immunotherapy [26] and a deviation from a Th2 to a Th1 immune response occurs [24, 27, 28]. In veterinary medicine, less is known about the mechanism of AIT, but what is known correlates well with what is described above. Hites and Hou et al. could show an increase in allergen-specific IgG4 antibodies after AIT [29, 30]. Keppel et al. showed an increase in FoxP3+ regulatory T cells and IL-10 and a decrease in allergen-specific IgE during AIT in dogs [31].

Allergen Selection

There are two ways to identify allergens involved in the disease process, which are later included in the AIT extract. One option is to test the animal intradermally by injecting allergens directly into the dermis and evaluate immediate or late reactions characterized by swelling and erythema at the injection site. Intradermal testing was considered the gold standard for many years, although false-positive reactions reported in several studies have raised doubts about this [32, 33]. Allergen-specific IgE serology testing is frequently performed in practice. Superiority of either test could not be conclusively shown [5]. It is now known that antibodies against cross-reactive carbohydrate determinants (anti-CCD IgE) can cause clinically irrelevant polysensitization to plant allergens and false positive serum test results (see article on IgE testing in this issue). A recent study showed that intradermal testing correlated well with serum testing in dogs with no detectable anti-CCD IgE or after blocking the anti-CCD IgE antibodies [34].

It is important to emphasize that both tests—IDT and serology—are tests unsuitable for the diagnosis of allergic disease. Although they both show a sensitization of an animal to a certain allergen, they cannot differentiate whether this sensitization is clinically relevant and causes the observed allergic symptoms. A thorough history focusing on

seasonality, environmental exposure, and duration of clinical signs is therefore crucial to decide which allergens are selected for AIT.

In a study performed by Willemse et al., dogs with atopic dermatitis based on hypersensitivity to environmental allergens in addition to house dust mite *D. farinae* did not improve with immunotherapy restricted to *D. farinae* alone [35]. They therefore concluded that desensitization should be customized to each patient and all allergens suspected to be relevant should be included. In contrast, Plant and Neradilek used a mixture of allergenic extracts selected based on regional aerobiology and abstained from intradermal tests or serum IgE assays. They could show that regional specific immunotherapy was safe and effective for the treatment of atopic dogs [36]. These published results to date seem to be contradictory and further prospective and larger studies are needed to clarify this topic.

Different Allergen Application Routes

For decades, AIT was applied subcutaneously (SCIT), but in the last few years, new routes for AIT such as sublingual (SLIT) [14, 15] and intralymphatic (ILIT) [16, 17] have been recommended.

In SCIT, allergens are injected subcutaneously starting with a low concentration and short injection intervals and gradually increasing concentration and time between injections. There are different protocols depending on the manufacturer and the allergens used. Aqueous allergens have to be injected more frequently as for example alum-precipitated allergen solutions, where monthly injections are sufficient. Most of the treated patients tolerate SCIT without any adverse effects and owners easily manage to inject their animals by themselves at home. However, those owners should be advised about how to monitor for possible adverse effects such as anaphylactic reactions and instructed what to do in such cases. Depending on the response and adverse effects, the protocol may have to be adapted to each single patient as needed.

SLIT is frequently and successfully used especially in human medicine for allergic rhinitis [37]. The mechanism of SLIT is based on the “oral tolerance system” [38]. With a high level of T regulatory cells and a high IL-10 cytokine milieu found in the oral mucosa, a tolerance response to most foreign antigens entering the alimentary tract can be achieved [38]. This immune response should result in the desired tolerance to orally applied AIT. What sounds very logical in theory seems to be difficult to achieve in canine atopic patients. Human patients are accurately instructed to ensure a long contact time between allergen (given as a solution or tablet) and mucosa. Swallowing, drinking, and food intake are prohibited for several minutes. Similarly, detailed instructions have to be given to owners of allergic dogs regarding how to apply SLIT in

dogs. In normal protocols, a small amount of allergen is administered once to twice daily between lips and gums (see package inserts of Artuvet, Netherlands and Heska SA, Switzerland).

ILIT was shown to be an effective and safe AIT option for the treatment of atopic dogs [16, 17, 39]. Normally, a smaller amount of alum-precipitated allergens (0.1–0.2 ml) is injected directly into a lymph node, either guided by ultrasonography or by palpation. Commonly, the popliteal lymph nodes are used, since they are easily palpable. In contrast to human medicine, where three intralymphatic injections lead to a long-term control of allergic symptoms, allergic symptoms in most dogs recur within some weeks to months after cessation of treatment [17, 40]. Therefore, the authors recommend to continue AIT after four intralymphatic injections (which equals 3 months of treatment) with monthly SCIT to keep the dogs in clinical remission.

Rush Immunotherapy

In rush immunotherapy (RIT), the induction period is abbreviated from weeks to just 1 or 2 days. To date, studies on rush SLIT and SCIT have been published [10, 41, 42, 43]. Dogs receive allergens hourly. In humans, the risk of anaphylactic reactions to RIT is still low but more common in venom RIT [44]. Therefore, it is recommended to perform AIT generally in a hospital setting [45]. In dogs, those reactions are rare; nevertheless, continuous monitoring is recommended and administration of antihistamines prior to RIT may be sensible. In a double-blinded study on RIT, there was no statistical significance that RIT is more effective than the normal SCIT protocol although additional concurrent medications were needed significantly less with RIT [41]. Although dogs have to be monitored closely in the clinic for half a day or a full day during RIT and it is more expensive, injections of allergen extract by the owner out of the wrong vial or in the wrong dose are minimized with this approach. In dogs with venom allergies, RIT seems to be a particularly good option to shorten the protocol time.

Use of Recombinant Allergens, Adjuvants, and Allergoids

One of the problems in veterinary allergology is the lack of standardization of protocols as well as allergens. A new product Allermune (ZENOAQ, Japan) combines a recombinant protein, Der f 2, and a pullulan adjuvant and consequently is suitable for house dust mite allergic patients only. This is the first licensed AIT in veterinary medicine using a standardized recombinant allergen. The treatment protocol differs from the ones mentioned above; six weekly injections are followed by

three monthly injections given by a veterinarian. The manufacturer states that this protocol will guarantee long-term improvement, but in the authors' experience, dogs relapse 2–3 months after cessation of Allermune therapy. Therefore, we advise to either continue Allermune every 4–6 weeks or change to long-term SCIT injections given by the owner. The big advantage of Allermune in comparison with ILIT, SCIT, and SLIT seems to be the very short time to improvement of approximately 2–6 weeks [20]. What exactly causes this rapid response is unknown at this time. Pullulan is a polysaccharide composed solely of glucose and is frequently used in the pharmaceutical, food, and cosmetics industries. It has been shown previously that pullulan can reduce IgE production and induce the production of blocking IgG antibodies, and therefore may reduce allergic reactions [46].

Another novel approach in veterinary and human medicine is the use of polymerized allergoids for desensitization. These allergoids are supposed to target dendritic cells, enhance allergen uptake through C-type lectin receptors, and may induce tolerance [47, 48]. A recent study by Gonzales et al. showed a 67% improvement of PVAS of DF-allergic dogs treated with allergoid coupled to no oxidized mannan over the first 3 months of treatment ($P < 0.0001$) [49].

Response to AIT

The efficacy of allergen immunotherapy for the treatment of canine atopic dermatitis was examined in a randomized study and several open studies and ranged from 50 to 70%, depending on the protocol designs and outcome measures used [5, 8–10]. We recently conducted a study comparing the efficacy of ILIT, SCIT, and SLIT. As outcome measure, we used a return-to-normal status and our results showed a clear advantage for ILIT with 60% (6/10) of dogs returning to normal compared with 16% (1/6) and 14% (1/7) of dogs receiving SCIT and SLIT respectively. This outcome measure is more stringent than the 50% improvement of clinical signs proposed as satisfactory in many other studies on AIT. Using this $\geq 50\%$ improvement of CADESI and PVAS with a stable or decreased medication score, 50% of dogs in the SCIT group and 80% of dogs in the ILIT group improved, whereas only 14% of the SLIT group showed improvement.

Dogs showed a good to excellent improvement of the clinical signs in 60% of HDM-sensitized atopic dogs treated with Allermune in Switzerland and Hungary [20]. In Japan, Kawano et al. found an even higher response rate in 85% (11 of 13) of treated dogs [21]. Therefore, Allermune seems to achieve response rates similar to those seen with ILIT. However, as there are fewer studies evaluating the newer treatment approaches with AIT compared with SCIT and patient numbers are still very limited, results need to be interpreted

with caution and further scientifically sound studies with larger case numbers are needed to confirm initial impressions.

Adverse Effects

Adverse effects with AIT are rare in dogs. Pruritus (by far the most common adverse effect), local swelling at the injection site, and listlessness have been reported [5]. Anaphylactic reactions that occasionally occur in human patients are uncommon in veterinary medicine [5]. Less than 1% of dogs treated with AIT show systemic signs such as diarrhea, vomiting, hyperactivity, urticaria, or apathy. There may be a higher risk of adverse effects in immunotherapy with bee or wasp venoms [50–52]. In those protocols or in patients, which have reacted to AIT previously, the prophylactic administration of antihistamines prior to AIT injection is recommended [50, 53••]. In case of adverse effects, glucocorticoids and/or antihistamines should be administered and the protocol should be adapted for the patient [53••]. With rare anaphylactic reactions, intravenous epinephrine may be needed and AIT should be discontinued or given under continuous clinical monitoring in a hospital setting.

Medication During Desensitization

Dogs treated with immunotherapy often need additional antipruritic medications to ameliorate clinical signs, particularly in the first months of treatment. Glucocorticoids and cyclosporine have significant effects on the immune system, particularly on lymphocytes, and therefore their use concurrent to AIT is controversial [54]. This topic has received little research in dogs. It may be sensible to avoid long-term administration of immunosuppressants in dogs receiving AIT [53••, 55•]. However, immunosuppressants may have little adverse effect on the response rate of immunotherapy, especially when use is limited to a short period at the beginning of AIT [53••, 56]. The authors attempt to limit the use of immunosuppressants as much as possible. A newer medication—occlacitinib—is often used in conjunction with AIT, due to its fast onset of action and good control of pruritus. Its immunosuppressive action has not been evaluated conclusively. However, a recent study showed that occlacitinib delayed epicutaneous sensitization in allergic dogs [57]. At this point, no in vivo or in vitro evidence exists to the authors' knowledge that shampoo therapy or the monoclonal anti-IL-31-antibody lokivetmab influences the outcome of AIT.

Conclusion

AIT is a good treatment option for canine atopic dermatitis and is the only etiological therapy available for this disease. During decades, AIT was applied subcutaneously (SCIT) using aqueous or aluminum-precipitated solution of allergens, but in the last few years, sublingual (SLIT) and intralymphatic (ILIT) administration are used more frequently. SCIT and ILIT combine a satisfactory success rate with a good safety profile. Anaphylactic reactions are rarely seen in animals. Pilot studies with different adjuvants to further increase safety and efficacy have been published. 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.

Compliance with Ethical Standards

Conflict of Interest Dr. Nina Fischer received a grant for an immunotherapy study from Albertheim Stiftung und Waltham.

Dr. Ralf Müller received financial support for studies about immunotherapy from Greer Laboratories, Artu Biologicals, and Heska Laboratories.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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