ALLERGEN-SPECIFIC IMMUNOTHERAPY IN CANINE ATOPIC DERMATITIS

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ABSTRACT

Canine atopic dermatitis is a multifactorial disease with multiple options of treatments. Allergen-specific immunotherapy is the only therapy that is able to change the course of the disease. Many studies have been published using allergen immunotherapy in dogs with atopic dermatitis. However, many differences on the study methodology make difficult a meta-analysis. The main routes used in allergen immunotherapy are the subcutaneous route, sublingual/oral route and intralymphatic route. The immunological changes aimed with allergen immunotherapy include a shift from Th2 to Th1-biased responses, an increase of regulatory T cells, IL-10 and TFG- ß, besides IgE suppression and increase of IgG andibodies. No severe adverse effects are seen in dogs under allergen-specific immunotherapy.

Key words: allergy; dogs; immunology

RESUMEN

La dermatitis atópica canina es una enfermedad multifactorial con múltiples opciones de tratamientos. La inmunoterapia específica de alérgenos es la única terapia que puede cambiar el curso de la enfermedad. Se han publicado muchos estudios utilizando inmunoterapia con alérgenos en perros con dermatitis atópica. Sin embargo, muchas diferencias en la metodología del estudio dificultan un metanálisis. Las principales vías utilizadas en la inmunoterapia con alérgenos son la vía subcutánea, la vía sublingual/oral y la vía intralinfática. Los cambios inmunológicos buscados con la inmunoterapia con alérgenos incluyen un cambio de respuestas Th2 a Th1, un aumento de células T reguladoras, IL-10 y TFG-ß, además de supresión de IgE y aumento de anticuerpos IgG. No se observan efectos adversos graves en perros en inmunoterapia específica con alérgenos.

PALABRAS CLAVE: alergía; perros; imunología

INTRODUCTION

Canine atopic dermatitis is defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features and commonly associated with IgE antibodies to environmental allergens (1). Although it is a multifactorial disease with numerous treatment options, allergen-specific immunotherapy (ASIT) is the only therapy that can modify the course of the disease (2). ASIT is defined by the World Health Organization as the practice of a gradual and increasing administration of an allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure do the causative allergen (3). To this time, there are several studies using ASIT in the treatment of canine atopic dermatitis. However, a variety of open and uncontrolled studies with different protocols, methods and other variables make difficult to compare results and to state a standard regimen in dogs with atopic dermatitis. There are no differences between allergen tests used for screening allergen composition, with similarities observed whether used *in vivo* intradermal test or whether *in vitro* IgE serology (4). The objective of this article is to make a brief review on published literature regarding ASIT in atopic dogs. Although there are some few studies using food allergen-specific immunotherapy, this review is based on ASIT against environmental allergens.

LITERATURE REVIEW

Mechanism of action

Canine atopic dermatitis is characterized by an immunological dysfunction with up-regulation of Th2, Th1, Th17 and Th22 responses, and increasing expression of cytokines and chemokines, such IL-4, IL-5, IL-13, IL-31, IL-33, IL-22, IL-17, thymus and activation-regulated chemokine (TARC/CCL17), thymic stromal lymphopoietin (TSLP) among others (5,6,7).

The immunological changes observed in dogs under ASIT are synthetized in figure 1. The aim of allergen-specific immunotherapy is the induction of peripheral T cell tolerance, characterized by the production of regulatory T (Treg) cells and promote a shift from a Th2 to Th1-biased response (8). In dogs, this shift from Th2 to Th1 response was associated with an increasing level of interferon-gamma (IFN-), whereas IL-4 level was not changed (9).

An increase of FoxP3+ Treg cells was associated to allergen immunotherapy in two studies (10,11). Treg cells can produce IL-10, which is associated to tolerance, by suppressing the expression of Th cells and activated monocytes and macrophages, and down regulates MHC class-II molecules and antigen-presenting cells capacity (8). Although one study find a significant increase in serum IL-10 in dogs receiving immunotherapy (10), other recent placebo-controlled studies failed to associate increasing levels of this cytokine with allergen immunotherapy (11,12). Transforming growth factor-beta (TGF-ß) is another tolerance-associated cytokine, which has been significantly increased in dogs after immunotherapy (11), although other study failed to do such association when comparing dogs receiving immunotherapy and placebo (12).

IgE suppression and an increasing concentration of IgG antibodies are associated with immunotherapy in dogs in many studies (10,13,14,15,16). IgG can act as a blocking antibody when competing with IgE for the same allergen (15).

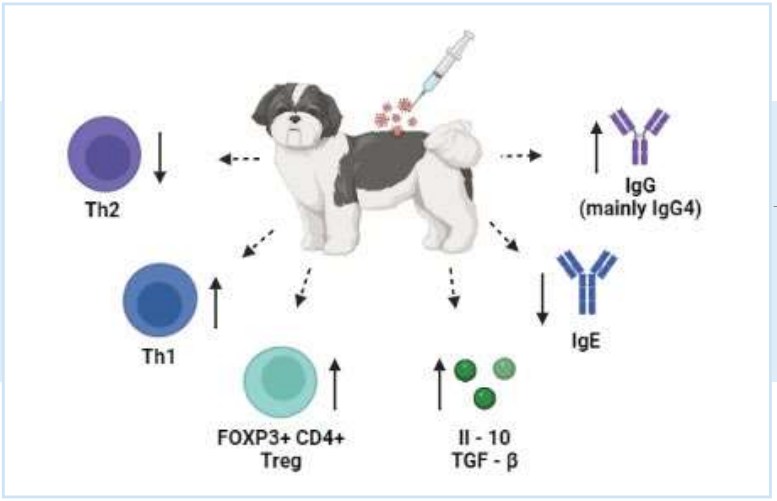

Figure 1. Expected immunological changes after allergen-specific immunotherapy in dogs.

Subcutaneous allergen-specific immunotherapy

The subcutaneous route is the standard route for injection of an allergen extract. Most of the studies of ASIT on atopic dogs use this route. Allergen extracts can be presented in aqueous solutions, which need more frequent injections, or with adjuvants, such aluminum hydroxide, which allow increasing the time between injections (17). Different protocols are available, depending of the manufacturer, but are generally divided into induction and maintenance phases. Maximal improvement can take one year after beginning and owners should be made aware (4). As ASIT is a long-term therapy with no immediate effects on clinical signs, owner compliance is essential for keeping the dog under therapy for at least 12 months and enhance the rates of success (18). Results of the success rate of subcutaneous ASIT from several published studies are disposed in box 1.

Box 1. Success rate of allergen immunotherapy in dogs with atopic dermatitis in several studies, using subcutaneous route. Adapted from Mueller, 2019 (4).

Study reference	Number of dogs	Success rate[a]
Scott et al., 1993 (19)	144	60%
Mueller and Bettenay, 1996 (20)	146	58%
Nuttall et al., 1998 (21)	186	22%
Zur et al., 2002 (22)	169	52%
Schnabl et al., 2006 (23)	117	64%
Plant and Neradilek, 2017 (24)	103	57%
Fennis et al., 2020 (25)	664	60%
Han et al., 2020 (26)	37	35%

a Percentage of "good to excellent" improvements.

Sublingual/oral immunotherapy

Sublingual immunotherapy relies on the fact that the patient needs to keep small amounts of allergens under the tongue for minutes before swallowing. This is feasible for humans, but not for dogs. In dogs, the extract is applied between the lips and gums once or twice a day. For this reason, oral immunotherapy is the best term for animals (4). This route induces a local immune response in the oral cavity to promote a tolerogenic environment, reducing Th2 polarization, through the allergen uptake by tolerogenic dendritic cells (27) Oral immunotherapy for the control of spontaneous canine atopic dermatitis has a success rate similar to subcutaneous ASIT (15), although a recent study demonstrated a lower success rate after 12 months when compared to subcutaneous and intralymphatic routes (28). The authors suspected that this lower response was related to inadequate contact time between the medication and oral mucosa (28).

Rush immunotherapy

With subcutaneous rush immunotherapy, the induction phase is given in 1 day, with allergens injected hourly and dogs monitored clinically in the hospital or veterinary clinic (4). A study showed 70% of good to excellent response in dogs with atopic dermatitis using aluminum-precipitated allergen extracts (29). It is recommended to give an antihistamine 1 to 2 hours before the injection of an allergen extract (4). It seems to be well tolerated in dogs, although it may increase pruritus (29,30).

Intralymphatic immunotherapy (ILIT)

Intralymphatic route is based on the injection of the extract directly in a lymph node, in order to reduce the time of the induction phase and enhance owner compliance (31). Previous studies showed that monthly injections of aluminum-precipitated allergen extract might reduce clinical scores in few months and provide long-

lasting effects in some dogs, with no major adverse effects (31,32). A recent study compared ILIT to subcutaneous and oral immunotherapies in dogs with atopic dermatitis (28). This study showed that dogs under intrapymphatic route had a higher return to normal rate compared to dogs under the other routes, in a 12-month follow-up (28). Finally, other study compared the efficacy of ASIT after an induction phase with ILIT and rush immunotherapy, with similar positive results on both alternatives (33).

Advances in allergen immunotherapy in dogs

Modern researches use new adjuvants, allergoids and recombinant allergens. These researches aim to develop products that have a shorter induction phase and a faster period for beneficial achievement.

The Allermune HDM (Nippon Zenyaky Kogyo – Zenoaq; Fukushima, Japan) is a subcutaneous immunotherapy with recombinant Der f 2 adjuvanted with the maltotriose polymer pullulan, already available on veterinary market. The first study used eight dogs experimentally sensitized to recombinant Der f 2, a low-weight *Dermatophagoides farinae*-derived allergen (34). In this study, six of eight dogs received Allermune immunotherapy under manufactures instructions, whereas two dogs received placebo. After 25 weeks, dogs receiving immunotherapy presented skin lesion scores significantly lower than dogs receiving placebo, with no adverse effects (34). Other study showed clinical benefits in the majority of the dogs on day 120 after beginning immunotherapy, with important reductions in the pruritus, skin lesions and the use of glucocorticoids (35). A third study showed the same beneficial responses in most of dogs as early as day 42 (36). It is interesting to note that on these two last cited studies, most of the dogs were sensitized to multiple allergens besides *D. farinae.*

Another novel allergen agents used in immunotherapy include glucotaraldehyde-polymerized allergoids conjugated with mannan (PM-allergoids). These allergoids target dendritic cells and enhance allergen uptake (37). A study used PM-allergoids from *D. farinae* for ASIT in *D. farinae*-sensitized atopic dogs, demonstrating reduction in pruritus and medications stores in a short period (few months), with no major adverse effects (37).

Adverse effects

ASIT is a very safe therapy. The most common adverse effect is an increased pruritus after allergen administration. Other very uncommon clinical signs may include localized injection reaction, anxiety, depression, hyperactivity, sleepiness, diarrhea, vomiting, urticarial, angioedema, weakness and anaphylaxis (4).

Conclusions

Allergen-specific immunotherapy is the only treatment for canine atopic dermatitis which can modify the course of the disease. It is a safe, medication-sparing therapy. The use of new adjuvants, allergoids and recombinant allergens seems to improve this kind of treatment, reducing time for clinical benefits and increasing owner compliance.

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