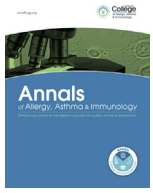
Ann Allergy Asthma Immunol xxx (2016) 1–6

Contents lists available at ScienceDirect



Review

Dog allergen immunotherapy: past, present, and future

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ARTICLE INFO

Article history:
Received for publication October 1, 2015.
Received in revised form November 25, 2015.
Accepted for publication December 2, 2015.

ABSTRACT

Objective: To review the published medical literature on dog allergy immunotherapy and discuss prior clinical trials, important allergens, extract specifics, and potential future treatment options for dog allergy relevant to the clinical allergist.

Data Sources: MEDLINE search was performed using the terms *dog, immunotherapy*, and *allergy* limited to human studies from any period. Articles cited in selected studies also were reviewed for appropriateness of inclusion into this review.

Study Selections: Publications were included that were original research and fit the topic of dog allergen immunotherapy, specifically articles that investigated prior effectiveness and safety of dog allergen immunotherapy, dog extracts, identification of dog allergens, and current prescribing trends among allergists.

Results: Two hundred fifteen articles were initially identified and 60 were reviewed in complete detail for inclusion in this review. The primary focus was placed on the 17 clinical trials that investigated the safety and efficacy of dog immunotherapy and the 19 studies that explored and defined the complex allergenic profile of dog extracts.

Conclusion: The medical literature on the use of dog extract immunotherapy in patients with hypersensitivity to dog shows poor and conflicting results of clinical efficacy, which has been attributed to poor-quality extracts and the inherent complex allergenic profile of dogs that remains without a clearly dominant allergen.

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Introduction

According to the American Pet Products Association, dogs currently live in more than 54.4 million US homes, and studies have shown that Can f 1 is nearly ubiquitous in public places.[1] Domesticated dogs initially fulfilled a pragmatic role for people, for protection or for agricultural use, but now serve a more emotional role of companionship. With this paradigm shift, dogs have moved indoors and constant exposure is associated with the development and exacerbation of allergic disease. For the patient with dog allergy, avoidance is clearly the best treatment modality, but this frequently does not occur even in settings beyond occupational allergy. The sensitization rate is reported as high as 10% of all people in Westernized countries,[2] and this rate varies by country, time period, and atopic predisposition.[3–5] As such, great efforts have been made in determining ways to minimize dog allergen levels in the home without removing the dog. Specific trials have looked at frequent washing of the dog,[6] using high-efficiency particulate air-filtered vacuum cleaners,[7] using high-efficiency particulate air room air filters,[8] and even breeding "hypoallergenic" dogs[9] or consistently altering their natural hair length.[10] All these methods can lower allergen levels but have failed to resolve the issue of dog allergy. Therefore, the allergist is presented with the option of recommending dog immunotherapy to help ameliorate patients' symptoms. This article reviews the current evidence on which to base this decision.

Early Clinical Studies

After the advancement in protein extraction methods in the early 1960s, it was hypothesized that the role of immunotherapy would expand far beyond pollens in the treatment of allergic disease. Soon after, reports were published about symptomatic improvement for patients with dog allergy after immunotherapy with the newest form of dog extract. The oldest report of successful dog immunotherapy was a presentation by Gould[11] in 1963, who reported a case series of 11 patients with dog allergy whose symptoms were alleviated after being treated with dog extracts. In 1967, Tuft and Torsney[12] reported that 13 of 17 patients (76%) with dog allergy had improved tolerance to dog exposure after immunotherapy, and Scherr[13] reported improved tolerance in 25 of 27 patients (93%) treated with dog extracts. However, no placebo injection or blinding controlled these trials and the improvement was based solely on subjective symptom scores.

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Disclosures: Authors have nothing to disclose.

Disclaimer: The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Air Force or the Department of Defense.

http://dx.doi.org/10.1016/j.anai.2015.12.006
1081-1206/Published by Elsevier Inc. on behalf of the American College of Allergy, Asthma & Immunology.

Although these early results were encouraging, clearly there was a need to improve the quality of evidence to support the use of dog allergen immunotherapy. As more data accumulated, the excitement for the effectiveness of this therapy began to wane. In 1968, Brown and Wolfe[14] prospectively compared immunotherapy with alum-precipitated dog extracts with the previous standard aqueous extracts in 50 patients with dog allergy. The 2 groups showed less convincing results because only 11 of 38 patients (29%) in the alum group and 4 of 12 patients (33%) in the aqueous group experienced any subjective improvement. No comparable control group was available to evaluate for potential placebo effects. To refute these negative results, Tuft and Torsney[15] reported additional information in 1976 regarding their continued experiences with dog immunotherapy with an additional 67 patients. A total of 62 of 84 patients (74%) subjectively reported increased tolerance to dogs, but there were no objective end points or placebo control group with which to compare these results.

First Double-Blinded Placebo-Controlled Trial

To aid in clarifying these conflicting data, the first randomized, double-blinded, placebo-controlled trial regarding the effectiveness of dog immunotherapy was published in 1984 and involved 27 children with asthma and dog allergy. Fifteen patients were placed on dog dander extracts and 12 received placebo injections containing histamine. The patients' responses were evaluated by bronchial and conjunctival provocation challenges and symptom scores. After 12 months of immunotherapy, 12 of 15 patients (80%) had improved tolerance to the conjunctival challenge compared with 2 of 12 (17%) who received placebo, 6 of 15 patients (40%) had improved tolerance to dog allergen bronchoprovocation compared with 2 of 12 (17%) who received placebo, and 8 of 15 patients (53%) had improved by subjective symptoms compared with 6 of 12 (50%) who received placebo. The only statistically significant difference for immunotherapy compared with placebo was noted to the conjunctival challenge because there was no difference in symptom scores.[16] Early laboratory methods of comparing specific immunoglobulin (Ig) E did not significantly change, but specific IgG increased significantly. The overall lack of improvement in asthma was postulated to be due to poor extract quality or confounding allergens, such as cat, for which this study did not control.[17]

The "Landmark" Dog Immunotherapy Trial

After further refinement in pet dander extracts, the landmark trial in dog allergy immunotherapy occurred in Denmark and initial results were published in 1986. This study compared 7 patients with asthma and dog allergy (and 15 with cat allergy) with 17 patients receiving placebo injections. The primary outcomes of investigation were symptom scores, bronchoprovocation testing reactions to dog allergen extract and histamine,[18] skin prick testing reactions, specific IgE level, and specific IgG and IgG4 levels.[19] At the end of 12 months of therapy, 4 of 7 patients (57%) with dog allergy reported improvement in symptoms and could tolerate roughly 3 times more conjunctival allergen (determined not to be statistically significant) but could not tolerate additional histamine levels by bronchoprovocation. Skin prick testing to dog extracts showed significantly decreased wheal diameter throughout the study in all patients who received immunotherapy. Specific IgE levels increased significantly in all patients receiving cat or dog immunotherapy during the first 9 months of therapy but began to decrease in the following 3 months in adults, whereas they continued to increase in children, which could be secondary to the effect of immunotherapy or natural exposure to allergen. Specific IgG and IgG4 levels also significantly increased in all patients. Importantly, no correlations between any laboratory measurements and symptom scores or allergen-specific bronchoprovocation testing were noted.

At the end of the initial 12 months, the blinding code was broken and the 4 patients with dog allergy receiving placebo were offered immunotherapy for 3 years (a total of 11 patients). After 2 years of immunotherapy, no significant change in outcomes was noted compared with just 1 year of treatment.[20] At completion of 3 years, symptom scores improved in 4 of 9 patients (44%) and allergen-specific bronchoprovocation testing (mean provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% of 0.2 mg/mL) and skin prick testing (mean wheal from 5.9 to 4.2 mm) results significantly improved, whereas nonspecific histamine bronchoprovocation testing failed to show a meaningful decrease in bronchial hyperreactivity. All improvements were noted in the first year and failed to improve further with additional treatment duration. There was no significant change in specific IgE when comparing pretreatment with post-immunotherapy values, and the diminutive increase in allergen-specific bronchoprovocation tolerance was unlikely to be clinically relevant.[21]

For patients who had received 3 years of dog immunotherapy, a 5-year follow-up evaluation was completed. Of the final 11 patients who had received dog immunotherapy, 9 patients responded to the symptom questionnaire, 6 agreed to the allergen challenge, 7 agreed to the histamine challenge, and 7 agreed to additional blood testing for IgE and IgG4. Three of the 4 patients who noted symptomatic improvement at the end of the 3-year study maintained this improvement 5 years later, whereas 1 patient noted worsening after discontinuing immunotherapy. Five of the 6 patients who underwent allergen-specific bronchoprovocation testing experienced an increase in sensitivity 5 years after the cessation of treatment compared with their bronchoprovocation testing results at the end of 3 years of immunotherapy. Specific IgG4 had decreased and specific IgE remained low at levels comparable to the end of 3 years of treatment. There was no correlation with the changes in immunoglobulin levels, bronchoprovocation threshold, and symptom scores.[22] The 2 major limitations of this study were that it was likely underpowered to find a difference in the predefined outcomes and that after the first year of treatment, there was no longer a placebo group with which to compare further results. The lack of efficacy noted and lack of placebo with which to compare the results lead to a study conclusion that does not support the use of dog immunotherapy.

Notably, the parallel cat immunotherapy arm showed a statistically and clinically significant difference in specific allergen and nonspecific histamine bronchoprovocation. Speculation continued that these findings most likely resulted from potency differences between the cat and dog extracts. The lower local and systemic side effect profile in the dog group also coincided with this theory, but similar immunologic changes in IgE and IgG levels in the dog and cat groups suggest otherwise.

Further Dog Immunotherapy Clinical Studies

Subsequent studies evaluated different hypotheses of why dog immunotherapy did not exhibit robustly successful results. Previously it had been proposed that only the late response is improved with therapy; however, a 1988 study showed that after immunotherapy, 3 of the 5 patients experienced complete inhibition of their immediate response and 1 patient with the dual response experienced ablation of early and late responses.[23] In 1989, another Danish study aimed to evaluate the effects of dog or cat immunotherapy in addition to maximal medical therapy alone (because it was deemed unethical to stop all other treatments) in 27 children with asthma. A statistically significant difference was found in an increased tolerance of dog allergen during bronchoprovocation