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Immunotherapy for pet allergies

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Abstract

Allergic diseases compose a serious challenge for modern societies. Their individual, medical and economical burden is large. As humans spend most of their time indoors, exposure to indoor allergens is a significant contributor to the development of allergic sensitization and respiratory allergies, such as allergic rhinoconjunctivitis and asthma. One important source of indoor allergens are pets, in particular cats and dogs. Allergens from these and other mammals spread effectively and they are encountered widely in public places. If patient education, allergen avoidance and pharmacotherapy do not suffice for controlling the symptoms of pet allergy, allergen immunotherapy can be a treatment option. Current information on allergen immunotherapy in pet allergy suggests that it can be effective in reducing allergic symptoms. However, the low number of high-quality randomized controlled trials of allergen immunotherapy in pet allergy warrants for further investigations.

Introduction

Allergic diseases are a serious health problem in westernized countries. Several factors associated with modern life style, such as the use of antibiotics, high-level hygiene, no exposure to farming-related microbes or the lack of certain infections, appear to be involved in promoting the development of allergic diseases.¹ According to a recent study, some 30-50% of Europeans showed a positive skin prick test result to at least one of the allergens examined², indicating a widespread diathesis for allergy. This predisposition, atopy, is a genetic property of an individual to mount an IgE response to innocuous environmental substances, allergens, and thereby become sensitized to them.

The hallmark of IgE-mediated allergy is the immediate allergen-provoked reaction in which mast cells and basophil granulocytes release a variety of immune mediators in minutes.³ Depending on the site of the reaction, the symptoms derive, for example, from gastrointestinal tract, eyes, airways or systemically. Respectively, they manifest as food allergy, allergic rhinoconjunctivitis, allergic asthma or anaphylaxis. In the long run, persistent allergic inflammation can lead to irreversible consequences, such as airway tissue remodeling in asthma.⁴ It is estimated that the prevalence of allergic rhinitis is 10-40% and it is often associated with asthma, in 15%-38% of the cases.^{5,6} As the diseases often coexist⁴, it is presumed that they represent a single entity.^{4,7} Allergic rhinitis is an important risk factor for allergic asthma.^{4,7}

The treatment of respiratory allergies requires a comprehensive approach in order to obtain a successful outcome for a patient. Therefore, it consists of patient education, allergen avoidance,

pharmacotherapy and, if indicated, allergen immunotherapy (AIT).⁷ In particular, AIT can be considered for those patients with allergic rhinitis who do not respond well to pharmacologic treatment.⁸ In allergic asthma, AIT is assessed to be effective and safe.^{8,9}

Pet allergens and allergen preparations

People easily come into contact with pet allergens, as pet ownership is very common. For example, it is estimated that about half of the households in Great Britain have either at least one cat or dog, and the populations of these animals are around 10 million or more.¹⁰ The highest densities of the pets are found in metropolitan areas. In addition to allergens from cats and dogs (Table 1), sensitization to horse allergens is common because of riding as a hobby.²² Other common sources of pet allergens are mice, rats, guinea pigs, gerbils and rabbits. Sensitization to animal allergens, especially to those from rodents, can also result from housing conditions^{23,24} or occupational settings.²⁵ Importantly, exposure to pet-derived allergens does not require a direct contact with the animals, as the allergens are widely present in homes without pets, schools, day care centers and other environments²⁶, at levels able to sensitize and cause symptoms.²⁷

Although molecular allergology has progressed vigorously in identifying, isolating and producing allergens (allergenic molecules/components) in a recombinant form from a variety of sources, including pets²⁸, in the past 20-30 years, AIT is still based on characterized and standardized allergen extracts.²⁹ In general, allergen extracts are prepared by suspending the raw material, for example defatted animal dander, in aqueous solution at neutral pH to allow allergens to dissolve, followed by centrifugation and dialysis to remove unwanted material.^{29,30}

The extracts need to fulfill several requirements to be reliably and safely used in AIT. These include, for example, composition, allergenic potency and stability.³¹ Of note, commercial providers indicate the potency of their products in their own units preventing comparability. Reference materials are expected to clarify the situation.³¹

Allergic sensitization to pets

Cat and dogs are among the most common sources of aeroallergens in the human environment.² Of interest, sensitization to dog was found to be as common as sensitization to cat in many parts of Europe. On average, the prevalence of sensitization to cat or dog was around 20% in adults below 45 years and around 13% in adults over 45 years.² A proportion of individuals are sensitized to more than one animal. In an unselected population-based birth cohort, analyzed by IgE reactivity to cat and dog allergens, the prevalence of sensitization to cat only was 11%, to both cat and dog 11% and to dog only 3% among 16 year-old subjects.³² However, it is often hard to know whether multiple sensitizations observed represent cosensitization or cross-sensitization, at least without detailed information on disease history and specific IgE determinations to pure (recombinant) allergens.³³ Basically, it can be thought that cross-sensitization is possible when allergens show a high degree of sequence similarity, as is the case between animal serum albumins or certain lipocalin allergens, such as cat Fel d 4, horse Equ c 1 and dog Can f 6.^{15,28} Specific IgE to some allergens, for example cat Fel d 1 or dog Can f 1/2, is considered a specific marker of sensitization to the respective animal.³⁴ In all, sensitization to multiple animal allergens is associated with increased bronchial inflammation in severe asthmatics.³⁵

Allergic sensitization is a complex immunological process involving a myriad of host-related factors, such as epithelial barriers, innate and adaptive immunity, and genetics, as well as environmental factors, which all together contribute to the development of an inappropriate response to innocuous environmental substances, allergens, and the production of specific IgE.³ This complexity is illustrated in a phenomenon designated as the modified Th2 response³⁶ which is also discussed.^{37,38} According to the hypothesis, the dose-response relationship between exposure to the cat allergen Fel d 1 and sensitization to it is bell-shaped. So, the highest level of sensitization is found in children exposed to the intermediate levels of the allergen, whereas tolerance would ensue at the higher levels of exposure. The protective effect is thought to involve the production of the regulative cytokine interleukin (IL)-10 and allergen-specific IgG4.^{39,40} Indeed, high respiratory antigen exposure appears to prevent allergic sensitization in an experimental human setting.⁴¹ Of interest, a recent report emphasizes the role of allergen-specific IgG1 (instead of IgG4) together with IL-10-producing regulatory cells in conferring protection against allergic symptoms.⁴² In addition to allergen dose, other factors related to allergens, such as the route and timing of exposure or the immune characteristics of the allergen, can contribute to allergic sensitization.^{1,37} For example, several mammalian respiratory allergens are lipocalins which have been found to be weakly antigenic/immunogenic, a feature associated with the development of allergenic T-helper type 2 response.⁴³

While it is obvious that a pet-allergic subject should avoid exposure to pets, for example, at home or workplace for not exacerbating the disease, routine avoidance to pets is not

recommended to infants and preschool children for reducing the risk of developing allergy or asthma.⁵ Indeed, it seems that exposure to pet allergens in early childhood does not predispose to the development of an allergic disease^{44,45}, although the situation can be more complex with rabbit and rodent allergens.⁴⁶

Mechanisms of immunotherapy in respiratory allergies

The modes of immunotherapy practised clinically, that is, subcutaneous allergen immunotherapy (SCIT) and sublingual immunotherapy (SLIT), for treating diverse respiratory allergies are thought to involve similar mechanisms of action.⁴⁷ They target multiple cell populations of the immune system, such as mast cells, basophils, eosinophils, dendritic cells, T cells and B cells. For example, the recruitment of eosinophils and mast cells/basophils has been found to be decreased within the site of inflammation following the therapy.^{48,49} Importantly, the development of a regulative immune response to allergen, mending the erroneous allergenic T-helper type 2 (Th2) immunity, is crucial for a successful immunotherapeutic intervention. Here, dendritic cells can be important, as AIT has been observed to promote their anti-allergenic properties.^{50,51} In line with this, regulatory dendritic cells, marked by the expression of the complement component C1q, upregulated in successful AIT, can be directly anti-inflammatory.⁵² They also support the differentiation of CD4⁺ T cells secreting suppressive interleukin IL-10. In general, various regulatory cell populations, such as IL-10 (Tr1) and transforming growth factor (TGF)- β -producing CD4⁺ T cells or IL-10-producing B cells (Br1), play a fundamental role in mediating the beneficial effect of AIT (reviewed in ⁴⁷). Moreover, AIT can result in the deletion of allergen-specific Th2 cells and thereby change favorably the balance between Th2 and

Th1/Tr1 cells.⁵³ Finally, AIT induces the synthesis of allergen-specific antibodies, in particular, IgG1, IgG4 and IgA.⁵⁴⁻⁵⁶ Although their role for the outcome of AIT is discussed, especially allergen-specific IgG4 is thought to function as a blocking antibody.^{57,58}

Allergen immunotherapy for pet allergies

General aspects

Conventional AIT (SCIT) is conducted by administering a series of injections of a relevant allergen preparation subcutaneously by trained medical staff.^{7,8} In the past 20-30 years, another form of AIT, SLIT, has gained increasing popularity.^{8,59} In SLIT, allergen preparation is administered as drops or dissolving tablets under the tongue for 1-2 minutes at home.⁵⁹ In general, AIT continues for three to five years.⁸ As the clinical indications for SCIT and SLIT largely overlap, SLIT, if available, may be preferable by some patients because of its convenience.^{7,8,59} However, SCIT tends to be a somewhat more efficient form of AIT than SLIT.^{9,60-62} Other modes of AIT than SCIT and SLIT, for example, intralymphatic or peptide-based AIT, are not discussed here, as they are basically experimental.⁶³

In considering patients for AIT, a crucial point is to set a proper diagnosis of an IgE-mediated disease by assessing the history of symptoms upon exposure to the allergen source and demonstrating clinically significant positive skin prick test and/or specific IgE results.⁷ Then, if the allergic rhinoconjunctival and/or asthma symptoms remain inadequately controlled, regardless of proper pharmacotherapy and allergen avoidance, AIT can be considered. In animal allergy, this can be an option if exposure to animal allergens cannot be prevented, for example,

because of the patient's profession (veterinarian, police officer, etc.) or environmental circumstances.⁶⁴ As to the safety of AIT, SCIT and SLIT contain a risk for adverse reactions, even anaphylaxis, and AIT for pet allergy does not make an exception (Table 2). Therefore, the medical personnel involved must be prepared for their management.^{7,8} With both modes of AIT, local reactions are relatively common.⁸ They include redness, pruritus and swelling at the injection site in SCIT or oropharyngeal pruritus and/or swelling in SLIT. Systemic reactions to AIT can be of variable seriousness, from mild ones up to anaphylaxis.^{65,66} While their occurrence in SCIT varies in different studies, one analysis found that it was approximately 0.2% per injection with conventional schedules.⁶⁵ In SLIT, the safety profile is very favorable.^{66,67} The contraindications of AIT include, for example, serious immunological diseases, severe or poorly controlled asthma and significant cardiovascular diseases.^{7,8}

Because there are a number of review articles and position papers concentrating on the outcome of AIT^{8,67}, only a few aspects are reviewed here. In general, AIT of patients with allergic rhinitis has been found to improve nasal and ocular symptoms, reduce the use of medication, improve the quality of life, prevent progression to asthma and reduce new sensitizations.^{8,61,68-73} In allergic asthma, the situation is more complex, and this may result from the heterogeneity of the disease.⁸ However, reviews of randomized controlled trials (RCT) found moderate to high evidence that AIT (SCIT and SLIT results combined) reduces asthma symptoms and medication use.^{62,72} In children, the reduction of symptoms was to some extent weaker than in adults. One of these reviews also assessed lung function and bronchial reactivity.⁶² As to the former, a large effect on small airways was shown. As to the latter, allergen-specific airway hyperreactivity was

found to be reduced effectively (SCIT studies only) whereas the analysis of nonspecific airway hyperreactivity showed a small effect favoring AIT. The reviews of RCTs focusing on SCIT concluded that asthma symptoms and medication were significantly reduced following the therapy.^{71,74} Moreover, allergen-specific bronchial hyperreactivity was reduced with less effect on nonspecific reactivity.⁷⁴ No consistent effect was observed on lung function.⁷⁴ While a review of RCTs focusing on SLIT found strong evidence that the therapy improves asthma symptoms with moderate evidence supporting the reduction of asthma medication⁷³, another review on SLIT reported nonconclusive results.⁷⁵

Allergic rhinitis and sensitization to pets

One important point to pay attention to is that the great majority of high-quality RCTs have investigated AIT in allergies to pollen or house dust mite. In consequence, the meta-analyses conducted reflect the outcome in those conditions. As the number of AIT studies in animal allergies is very small, it has been pointed out that confident conclusions regarding the therapy cannot be drawn.⁷ For example, a recent systematic review of double-blind RCTs of AIT for allergic rhinitis reported no SCIT study with a conventional allergen extract in animal allergy.⁶¹ In two other reviews of RCTs^{71,72}, altogether three studies on cat allergy were included. One of these, the study of Alvarez-Cuesta et al., found that the treatment of cat-allergic subjects with rhinoconjunctivitis and asthma with a standardized cat allergen extract resulted in the statistically significant improvement in the medication-symptoms score, allergen bronchoprovocation test, conjunctival provocation test and skin prick test after one year of therapy.⁷⁶ Nonspecific bronchial hyperreactivity with methacoline was marginally improved and the change was not statistically significant. In the study of Varney et al., the group of subjects with allergic

rhinoconjunctivitis and asthma actively treated with cat allergen extract exhibited a marked reduction in the symptom score (nasal and other symptoms combined) and a reduced fall in peak flow upon cat exposure.⁷⁷ The changes were statistically significant. Moreover, the conjunctival provocation threshold increased and the immediate intradermal and the late-phase skin responses decreased significantly. Nanda et al. reported, for example, that the patients with allergic rhinitis with or without asthma symptoms upon cat exposure treated in the high-dose group with cat allergen extract exhibited a significant decrease in total early symptom scores on nasal challenge at one year.⁷⁸

Recent reviews of RCTs of SLIT for allergic rhinitis^{61,69,72,73} comprise two studies in animal allergy, that is, allergy to cat. Nelson et al. reported that the cat allergen extract-treated group of subjects with allergic rhinoconjunctivitis with or without asthma did not show significantly different results in symptom scores (ocular, nasal and respiratory symptoms) or nasal obstruction on cat allergen exposure on day 105 than the control group.⁷⁹ On the other hand, Alvarez-Cuesta et al. reported that cat-allergic patients with rhinoconjunctivitis with or without asthma treated with standardized allergen extract for one year showed significant improvements in all four symptom categories (total, nasal, bronchial and ocular) on cat allergen exposure whereas this was not case in the placebo-treated group.⁸⁰ Moreover, only the actively-treated group showed a significantly reduced peak expiratory flow response on cat allergen exposure and a significant improvement in the skin test reactivity with cat allergen extract.

Allergic asthma and sensitization to pets

The review of RCTs by Abramson et al. offers the most comprehensive collection of allergen extract-based SCIT studies in asthma due to sensitization to pets (cats and dogs)⁷⁴ compared to other recent reviews which do not contain additional studies.^{62,71,72} In the following, selected analyses from the placebo-controlled studies from the 1980s onward are discussed. Abramson et al. found that asthma symptom scores (standardized mean difference, SMD) in the three studies included were improved in two studies (SMD -2.27 (95% confidence interval (CI) -3.25 to -1.29) and -1.29 (CI -2.11 to -0.46)) whereas in one study (two references) there was a tendency for that (SMD -0.25 (CI -1.01 to 0.52)).^{76,77,81,82} Accordingly, AIT with animal allergen extract was favorable against symptomatic deterioration (SMD 0.47 (CI 0.24 to 0.92)), analyzed by four studies.⁸¹⁻⁸⁵ Analyses on medication did not contain studies with pet allergens, and the analysis of lung function parameters contained only one study.⁸⁴ It tended to show a favorable effect (SMD -1.01 (CI -2.04 to 0.02)). The analysis of nonspecific bronchial hyperreactivity indices contained three studies^{76,83,86}, out of which two tended to show a statistically significant favorable effect^{83,86} and one did not show any effect.⁷⁶ For the analysis of allergen-specific bronchial hyperreactivity indices, a total of six studies of animal AIT^{76,77,84-87} could be included (one of which was a study with cat allergen peptides⁸⁷, otherwise not considered here). The effect was favorable (SMD -0.61 (CI -0.95 to -0.27)). As to the adverse reactions in animal AIT in the review of Abramson et al.⁷⁴, the risk ratio (RR) in one study^{81,82} was 0.80 (CI 0.25 to 2.55) for local reactions whereas in two other studies^{84,85} it was 2.35 (CI 0.27 to 20.72) and 4.50 (CI 0.25 to 81.76). For the analysis of systemic reactions, three studies were eligible, and the risk ratios ranged from 1.20 (CI 0.27 to 5.29) to 3.56 (CI 0.49 to 25.59).⁸³⁻⁸⁵

Recent reviews of RCTs on SLIT virtually contain no studies for animal allergen-induced asthma^{62,72,73,75}, with the exception of that by Alvarez-Cuesta et al.⁸⁰, see the paragraph of SLIT for allergic rhinitis, above. Regarding this study, the analysis of Dhami et al. concluded that the bronchial symptom score was moderately improved (SMD -0.77 (CI -1.48 to -0.06)).⁶²

Conclusions and future prospects

A large body of evidence so far suggests that AIT (SCIT and SLIT) is a valuable tool for fighting respiratory allergic diseases. It complements the other arms of therapy, that is, patient education, allergen avoidance and pharmacotherapy, targeting the mechanisms accounting for allergy. Accumulating information points out, however, that it may be time to carefully analyze the existing data on AIT and to pinpoint the topics requiring further addressing. These issues include the effectiveness, cost-effectiveness and safety of SCIT and SLIT in treating allergic rhinoconjunctivitis and allergic asthma.^{9,88} In particular, additional studies of AIT for pet-associated respiratory allergies are needed, because, as shown in this article, their number is very low. Obviously, that makes difficult to draw more definitive conclusions of the role of AIT in pet allergies. Moreover, AIT studies in allergies to animals other than cat and dog would be welcome. Based on the current experience of AIT, it appears justified to note that AIT for pet allergies has good prospects to become wider recognized as a treatment choice in the future, possibly taking advantage of characterized recombinant allergens, novel adjuvants or alternative routes of delivery, for example, intralymphatically.⁶³

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Tables

Table 1. Characterized cat and dog allergens

Allergen	Biochemical name	Molecular mass (kDa)	Glycosylation	Prevalence of sensitization (%)	Key reference
<i>Dog (Canis familiaris)</i>					
Can f 1	lipocalin	22–25	yes	50-75	11
Can f 2	lipocalin	22–27	putative	25-40	11
Can f 3	serum albumin	69	no	35	12
Can f 4	lipocalin	16–18		35-60	13
Can f 5	prostatic kallikrein	33	yes	up to 70	14
Can f 6	lipocalin	20	putative	38-61	15
<i>Cat (Felis domesticus)</i>					
Fel d 1	secretoglobin	38	yes	>90	16
Fel d 2	serum albumin	69	no	20	17
Fel d 3	cystatin	11	putative	10	18
Fel d 4	lipocalin	20	putative	63	19
Fel d 5	IgA	400	yes	38	20
Fel d 6	IgM	800-1000	yes		20
Fel d 7	lipocalin	18	no	38	21
Fel d 8	latherin-like protein	24		19	21

Table 2. Features of selected randomized controlled trials discussed in this review

	Approach	Subjects	Regimen	Reported significant (p<0.05 or less) improvement in the actively treated group vs. control group	Reported adverse reactions
Alvarez-Cuesta E et al. 1994 ⁷⁶	SCIT, RCT, DB, PC, cat allergy	28, aged 15-28 yrs, A with RC	Cat dander extract, 1 yr	Medication-symptoms score, skin prick test, conjunctival provocation, allergen bronchoprovocation	Local reaction in 7 subjects and mild systemic reactions in 3 subjects in the actively treated group
Alvarez-Cuesta E et al. 2007 ⁸⁰	SLIT, RCT, DB, PC, cat allergy	50, mean age 27 yrs, RC with/without A	Cat dander extract, 1 yr	Total and nasal symptoms scores, PEF, skin test reactivity	No local or systemic reactions
Haugaard L et al. 1992 ⁸³	SCIT, RCT, DB, PC, cat and/or dog allergy	24, aged 13-48 yrs, A	Cat and/or dog dander extract, 5 mo	Symptoms of cat-allergic subjects on cat exposure	Local reactions in about 25% of all injections, some systemic reactions in both groups, 1 severe asthma reaction and 1 anaphylactic reaction in the actively treated group
Nelson HS et al. 1993 ⁷⁹	SLIT, RCT, DB, PC, cat allergy	41, aged 18-74 yrs, RC with/without A	Cat hair and epithelium extract, 105 d	Not observed	Similar number of mild reactions in both groups
Ohman JL et al. 1984 ⁸⁴	SCIT, RCT, DB, PC, cat allergy	17, aged 22-48 yrs, A	Cat pelt extract, 16 wk	Skin test reactivity, pulmonary symptoms score on cat exposure, subjective allergic symptoms, allergen-specific IgG	Large local reactions in 2 subjects and systemic reactions in 4 subjects in the

Sundin B et al. 1986 ⁸⁵	SCIT, RCT, DB, PC, cat or dog allergy	41, aged 8- 47 yrs, A	Cat or dog dander extract, 1 yr	Allergen bronchoprovocation	actively treated group, systemic reactions in 1 subject in the placebo group, all mild Systemic reactions in all 12 children at high allergen doses (build-up in rush IT), all mild, otherwise a few mild systemic or local reactions
Valovirta E et al. 1984 ⁸¹ , 1986 ⁸²	SCIT, RCT, DB, PC, dog allergy	27, aged 5- 18 yrs, A	Dog dander and hair extract, 1 yr	Conjunctival provocation, skin test reactivity, allergen- specific IgG	No significant difference in mild local reactions between the groups
Van Metre TE et al. 1988 ⁸⁶	SCIT, RCT, DB, PC, cat allergy	22, aged 21- 52 yrs, A	Cat hair and dander extract, 1 yr	Allergen bronchoprovocation, skin test reactivity, allergen-specific IgG	Mild systemic reactions in 2 subjects and large local reactions in 6 subjects in the actively treated group
Varney VA et al. 1997 ⁷⁷	SCIT, RCT, DB, PC, cat allergy	28, aged 19- 50 yrs, RC with A	Cat dander extract, 3 mo	Asthma symptom score, allergen bronchoprovocation	6 large local reactions in both groups, 3 mild systemic reactions in the actively treated group and 2 in the control group

SCIT - subcutaneous allergen immunotherapy, RCT - randomized controlled trial, DB - double-blind, PC - placebo-controlled, A - asthma, RC - rhinoconjunctivitis, SLIT - sublingual allergen immunotherapy