



Does evidence support the use of cat allergen immunotherapy?

Sangeeta Dhami^a and Arnav Agarwal^b

Purpose of review

Cat allergy can manifest as allergic rhinitis, conjunctivitis and/or asthma. With widespread cat ownership and exposure, cat allergy has emerged as a major cause of morbidity. Cat allergen immunotherapy is a potential disease modifying treatment for patients with cat allergy. We examine evidence on the effectiveness, cost-effectiveness and safety of cat allergen immunotherapy and consider the clinical contexts in which it should be prescribed.

Recent findings

The European Association of Allergy and Clinical Immunology systematic reviews on allergic rhinitis and asthma along with the accompanying guidelines on allergic rhinitis were used as primary sources of evidence. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are most common routes of administration for allergen immunotherapy (AIT). A limited number of high-quality studies related to cat dander have shown mixed results in improvements in ocular and nasal symptoms, asthma symptoms, peak expiratory flow rate and medication use scores with subcutaneous immunotherapy. Two studies examining cat dander and cat-related allergy response with sublingual immunotherapy have shown mixed results in terms of symptomatic response. One randomized trial examining intralymphatic immunotherapy has shown a positive symptom response and a favourable safety profile. Although studies have reported mixed results regarding safety of SCIT, adverse events have been reported more commonly with SCIT than SLIT.

Summary

There is a limited body of high-quality evidence on the effectiveness and safety of cat AIT and no high-quality data on its cost-effectiveness. The available evidence on effectiveness is mixed based on studying a limited array of immunological, physiological and patient-reported outcome measures. Based on this evidence and extrapolating on the wider evidence base in AIT, it is likely that some patients may benefit from this modality of treatment, particularly those with moderate-to-severe disease who are inadequately controlled on allergen avoidance measures and pharmacotherapy and those who are monosensitized to *Felix Domesticus* 1. Further evidence is, however, required from larger trials before more definitive advice can be offered.

Keywords

allergen immunotherapy, allergic asthma, allergic rhinitis, cat allergy, IgE-mediated allergy

INTRODUCTION

Allergic rhinitis, conjunctivitis and asthma are examples of IgE-mediated conditions that may have a number of allergic triggers, including cat allergy [1–3]. Cat ownership is widespread, particularly in westernized countries with, for example, estimates indicating that approximately one in five of UK households and one in three US households own one or more cats [4]. Exposure to small amounts of cat dander, urine and/or saliva, whether domestically from household pets or in other areas such as schools or the workplace, can trigger symptoms in sensitized individuals.

Allergen avoidance is the first-line measure in proven IgE-mediated cat allergy. Such a strategy may not, however, be acceptable to cat owning households and may, in any case, be insufficient in achieving complete allergen avoidance. Pharmacological reliever and preventer therapy with local/systemic

^aGP Returner Edinburgh, Edinburgh, UK and ^bPGY-1 Internal Medicine, University of Toronto, Toronto, Ontario, Canada

Correspondence to Sangeeta Dhami, GP Returner Edinburgh, Edinburgh, UK. E-mail: sangeetadhami@hotmail.com

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KEY POINTS

- Allergy to cats is increasing due to the ubiquitous nature of cats and their dander.
- Allergic presentations of cat allergy are primarily in the form of allergic rhinitis, allergic rhinoconjunctivitis and allergic asthma.
- The mainstay of treatment is allergen avoidance and pharmacotherapy.
- Where conventional management options are ineffective or unacceptable, limited high-quality evidence and recent guidelines suggest immunotherapy should be considered.
- Immunotherapy should only be initiated by a specialist following careful consideration of the pros and cons of the treatment.

antihistamines, beta-2 agonists, topical corticosteroids, mast cell stabilizers and antileukotrienes represent the mainstay of treatment for those with inadequate symptom relief despite allergen avoidance measures.

Allergen immunotherapy (AIT) is the only potentially disease-modifying therapy for IgE-mediated allergic disease [5–7]. AIT involves repeated, gradually incremental allergen exposure at specified intervals to the identified allergen. These exposures modulate the immune response with the goal of improved symptom control and a decreased need for rescue medications. The purpose of this review is to summarize evidence examining the effectiveness, cost-effectiveness and safety of AIT for cat allergy.

CAT ALLERGEN: FELIX DOMESTICUS 1

The major protein responsible for cat allergy is *Felix Domesticus* 1 abbreviated to Fel d1. It is unknown what function this protein serves for the cat, but in susceptible humans it is responsible for provoking an IgE-mediated allergic reaction [8]. There is recent interest in the role of the minor cat allergens Fel d2, Fel d4 and Fel d7 which may also be responsible for contributing to asthma caused by cat allergy [8]. Measurement of IgE to these components may be useful in identifying more specific allergen sensitization [8].

These allergens are found in the dander, saliva and urine of cats. They are readily transferred through adherence to surfaces such as clothing, soft furnishings, carpets and shoes, and also to small particles allowing airborne transfer of the allergen. For example, studies have shown the presence of the Fel d1 protein in school dust samples [9]. Only a

small amount of allergen is needed to elicit an immune response, and due to its ubiquitous nature and easy spread into public places, secondary exposure is common.

EPIDEMIOLOGY OF CAT ALLERGY

There are limited reliable data on the prevalence of cat allergy. Cat-related reactivity was the only pet allergen tested in both the National Health and Nutrition Examination Survey II and III, and increased 5.5-fold (3.1–17.0%) between the two studies, relative to a 2.6-fold increase in five other common allergens [10]. Allergy clinic-based studies suggest between 10 and 25% of patients are sensitized to cat allergen. Sensitization to cat allergen, however, only refers to the presence of IgE and not everyone who is sensitized will progress to develop allergic symptoms. These individuals are, however, more susceptible to develop clinical manifestations of allergic disease.

SOURCES OF EVIDENCE

The most recent systematic reviews published on allergic rhinitis, rhinoconjunctivitis and asthma are the European Academy of Allergy and Clinical Immunology (EAACI) systematic reviews and accompanying clinical guidelines on allergic rhinitis. These were drawn on to identify relevant evidence [11–15]. We only concentrate on higher order evidence from randomized double-blind placebo-controlled trials to assess clinical effectiveness and cost-effectiveness considerations. We also considered evidence from recent systematic overviews of systematic reviews on AIT for allergic rhinoconjunctivitis and allergic asthma [16,17].

ROUTES OF ADMINISTRATION OF ALLERGEN IMMUNOTHERAPY

Allergen immunotherapy can be administered through a number of routes. Traditionally, the subcutaneous (SCIT) route has been used, also referred to as injection immunotherapy. SCIT must only be administered in a specialist centre with access to full resuscitative facilities due to the risk of triggering potentially life-threatening anaphylaxis. Sublingual immunotherapy (SLIT) is an alternative, more convenient approach with potentially reduced risk of triggering anaphylaxis. This can be administered through drops at home. The intralymphatic (ILIT) route is another possible route of administration, although this remains largely experimental at present.

Table 1. Allergen-specific bronchial provocation tests in asthma patients postallergen immunotherapy

Reference	Bronchial provocation test	Summary
Alvarez–Cuesta <i>et al.</i> [21]	PC20 to Fel d1	Significant improvement in SCIT group compared with placebo
Ohman <i>et al.</i> [24]	PD20-FEV1-Cat	No significant difference between active and placebo groups
Pene <i>et al.</i> [25]	PD20-fev1-Fel d1	No significant difference between active and placebo groups
Sundin <i>et al.</i> [26]	LogPC20-FEV1-Cat	Significant improvement in active group compared with placebo
Taylor <i>et al.</i> [27]	PD20-FEV1-Cat allergen	All 5 SCIT patients showed a decrease in bronchial sensitivity
Van Metre <i>et al.</i> [28]	PD-20 Cat extract	Significant improvement in active group compared with placebo

Fel d1, *Felix Domesticus* 1; SCIT, subcutaneous immunotherapy. Adapted with permission [12[■]].

EFFECTIVENESS

Subcutaneous immunotherapy

A limited number of high-quality SCIT studies have been conducted to cat dander, which have shown mixed results. Patel *et al.* [18] conducted a double-blind randomized placebo-controlled, parallel-group trial using Fel d1 peptide in patients with allergic rhinitis due to cat allergy. They found a significant improvement in both ocular and nasal symptoms using the change in Total Rhinoconjunctivitis Symptom Score (TRSS) in those treated with cat AIT receiving four injections of 6-nmol 4 weeks apart compared with placebo, which persisted for up to a year after treatment completion [18]. However, the results from the Phase III trial using the same immunotherapy product (Cat-pad) was reported in 2016 and did not achieve its desired end-point. In fact the mean TRSS was improved in both the treatment and the placebo groups. There was no significant difference found in the combined symptom and medication score between active treatment and placebo arms [19].

Varney *et al.* [20] looked at 28 patients with moderate-to-severe allergic rhinitis and asthma to cats and found that in a double-blind, placebo controlled study a significant reduction in symptoms in the AIT group compared with the placebo group. They also found a reduction in peak expiratory flow rate response on exposure to cat in the active group [20].

In another trial of 28 mono-sensitized asthma patients aged 15–65 years, Alvarez-Cuesta *et al.* [21] examined SCIT for cat dander extract versus placebo. The trial found significant differences in short-term symptom and medication scores [21]. Significant differences in total number of days with asthma symptoms and need for asthma drug medication were also reported between SCIT for various allergens versus placebo from a trial of 20 monosensitized children by Cantani *et al.* [22]. Significant long-term effectiveness in controlling asthma symptoms in the paediatric setting have also been found relative to placebo in a large trial of 130 children polysensitized to multiple allergens, including animal dander [23].

Furthermore, several SCIT studies have reported on the effects of immunotherapy in terms of a range of bronchial provocation test responses. Six SCIT studies reported on allergen-specific bronchial provocation tests which showed mixed results (Table 1) [21,24–28] and five studies reported on nonspecific bronchial provocation tests (Table 2) [21,24,27–29] which all reported no significant difference between the active and placebo groups.

Sublingual immunotherapy

Two trials looking at cat dander or cat-related allergens with SLIT as an intervention were identified [30,31].

Table 2. Nonspecific bronchial provocation tests in asthma patients postallergen immunotherapy

Reference	Bronchial provocation test – outcome	Summary
Alvarez–Cuesta <i>et al.</i> [21]	PC20-MCh	Active group no difference, placebo group got worse. No comparison of active and placebo group reported
Haugaard and Dahl [29]	PC20-Histamine	No significant difference between active and placebo groups for Cat
Ohman <i>et al.</i> [24]	PD20-FEV1 MCh	No significant difference between active and placebo groups
Taylor <i>et al.</i> [27]	PD20-FEV1-Histamine	No significant change in active or placebo group
Van Metre <i>et al.</i> [28]	PD20-MCh	No significant difference in active compared with placebo group

Adapted with permission [12[■]].

Alvarez-Cuesta *et al.* [30] examined cat dander-based SLIT relative to placebo with 50 patients with allergic rhinitis some also with asthma monosensitized to cat dander. The study found a significant improvement in symptom scores in the AIT group compared with placebo [26]. They also found no adverse events were experienced by either group [30].

Nelson *et al.* [31] found many years earlier in a double-blind placebo controlled study conducted on 41 adult patients with allergic rhino-conjunctivitis some also with asthma symptoms on exposure to cats. SLIT was administered for 105 days using a high dose standardized cat extract [31]. Changes in symptom scores and nasal-blockage index were used to assess effectiveness before and after treatment [31]. There was no significant difference in symptoms and nasal blockage in the active group compared with placebo [31].

Intralymphatic

One randomized double-blind trial by Senti *et al.* [32], the first human trial using ILIT, was identified. This showed a positive response to immunotherapy assessed by nasal tolerance compared with placebo following administration of only three ILIT injections [28]. The safety profile of the treatment were also favourable [32].

COST-EFFECTIVENESS

There is currently no high-quality evidence formally investigating the cost-effectiveness of AIT for cat allergy.

SAFETY

Specific to cat allergen immunotherapy

Due to the limited number of studies looking specifically at cat allergy, the data in this area is also limited.

Subcutaneous immunotherapy

Varney *et al.* [20] reported no adverse effects. Patel *et al.* [18] reported a number of treatment emergent adverse events the majority of which were mild. Six adverse events led to subjects withdrawing from the study only one of which was felt to be related to the study drug which caused hypersensitivity [18]. Alvarez-Cuesta *et al.* [21] reported 14 adverse events in the intervention arm (1.9 reactions for every 100 injections administered) and three systemic reactions were treated with epinephrine. No adverse events were reported in the comparator arm [21].

Seven patients reported local adverse events [21]. Cantani *et al.* [22] reported no systemic reactions; no local reactions were reported in the active group, and one was reported in the placebo group.

Sublingual immunotherapy

Alvarez-Cuesta *et al.* [30] reported that no adverse events occurred in either the active or the placebo group. Nelson *et al.* [31] reported no serious adverse events with a similar number in both active and placebo groups. A number of local side-effects were reported, such as pharyngeal pruritus, more commonly in the active group [31].

Intralymphatic

The one trial quoted above had a good safety profile but data in this area is limited as ILIT is a more experimental treatment [32].

Generic safety of allergen immunotherapy with all allergens

A prospective European survey performed by EAACI with over 4000 patients revealed that both SCIT and SLIT were found to be safe in adult and paediatric populations, and only a small number of systemic reactions were associated with either [33,34].

CLINICAL IMPLICATIONS

Recent AIT guidelines from the EAACI AIT Guidelines Taskforce provide evidence-based recommendations using the Appraisal of Guidelines for Research and Evaluation-II approach, and based on a formal systematic review and critical appraisal of the literature [11¹¹–15¹⁵]. Evidence was synthesized around the effectiveness, cost-effectiveness and safety of AIT in patients with allergic rhinitis/rhinoconjunctivitis and asthma.

EAACI guidelines recommend AIT should be considered with symptoms strongly suggestive of allergic rhinitis/rhinoconjunctivitis or asthma, evidence of IgE-mediated sensitization to clinically-relevant allergens, or moderate-to-severe symptoms despite avoidance and pharmacotherapy strategies (Grade A for SLIT, B for SCIT). Given the long-term effects of AIT on rhinitis, therapy may be considered in less severe cases as well. Based on its synthesis of existing evidence, AIT was found to be effective for allergic rhinoconjunctivitis driven by animal dander [11¹¹–15¹⁵]. The British Society of Allergy and Clinical Immunology guidelines on immunotherapy for allergic rhinitis also recommend AIT can be used for cat allergy [35].

IMPLICATIONS FOR FUTURE RESEARCH

There is a need for work on the epidemiology of cat allergy, the need to better understand the natural history of this condition and its associated disease burden, and a need for large, high-quality placebo-controlled and head-to-head trials of SCIT, SLIT and ILIT. Such trials should study a range of immunological/physiological, clinical and health services outcomes. There is a particularly pressing need for robust health economic evaluations of cat AIT.

CONCLUSION

There is a limited body of high-quality evidence on the effectiveness and safety of cat AIT and no high-quality data on its cost-effectiveness. The available evidence on effectiveness is mixed based on studying a limited array of immunological, physiological and patient-reported outcome measures. Based on this evidence and extrapolating on the wider evidence base in AIT, it is likely that some patients may benefit from this modality of treatment, particularly those with moderate-to-severe disease who are inadequately controlled on allergen avoidance measures and pharmacotherapy and those who are mono-sensitized to Fel d1. Further evidence is, however, required from larger trials before more definitive advice can be offered.

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Conflicts of interest

S.D. is an author on the EAACI Systematic reviews on allergen immunotherapy in rhinitis and asthma and contributed to the EAACI guidelines on allergen immunotherapy in rhinitis. A.A. is a coauthor on the EAACI systematic review on allergen immunotherapy for rhinitis and contributed to the EAACI guidelines on allergen immunotherapy in rhinitis.

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