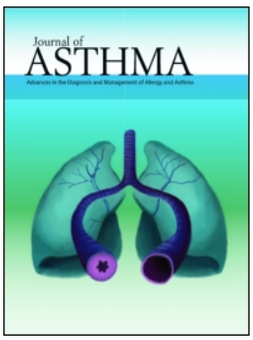

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Allergen immunotherapy in asthma: current evidence

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ABSTRACT

Background: Allergic asthma is the predominant phenotype in clinical practice. Allergen immunotherapy is the only curative and specific approach for the treatment of allergies with clinical benefits for several years after its discontinuation. Despite advances, the use of allergen immunotherapy in allergic asthma is still suboptimal and controversial.

Objective: The purpose of this article is to review the published data about the impact of allergen immunotherapy with the most commonly used allergen extracts on allergic asthma outcomes, including both clinical parameters and patients' subjective experience (quality of life).

Methods: As data sources several databases were used, including PubMed, Scopus, Web of Science (2002–2019) and search in English and Spanish languages was performed using the following terms: "allergen immunotherapy" and "asthma" in combination with "house dust mite", "birch pollen", "grass pollen", "olive tree pollen", "molds", "pets" and "asthma quality of life". Randomised control trials and meta-analysis from reviewed publications were selected.

Results: Emerging data relating to the positive impact on asthma outcomes of allergen immunotherapy allows the addition of this treatment as a therapeutic option in mild to moderate asthmatics sensitized to house dust mite and pollens. Limited data are available for patients sensitized to molds and pets, as well in severe allergic asthma population.

Conclusion: Allergen immunotherapy remains a potential therapeutic option for some patients with allergic asthma. Further research is needed to define the optimal period of treatment, the possible therapeutic role in the treatment of severe allergic asthma, and the cost-effectiveness of allergen immunotherapy in asthmatic patients.

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Introduction

Asthma is a heterogeneous disease with multiple phenotypes based on distinct pathophysiological mechanisms and represents a major public health problem with over 300 million people affected worldwide (1,2). Allergic asthma (AA) is the most frequent clinical phenotype (75–80%) (1) and allergen immunotherapy (AIT) added to controller treatment represents a therapeutic option (3).

Unlike conventional pharmacotherapy that is able to control symptoms and inflammation, AIT—sublingual (SLIT) or subcutaneous (SCIT)—could modify disease history by induction of immune tolerance to allergens *via* regulation of T- and B-cell-mediated IgE-dependent responses, and suppression of effector cells activation (mast cells, basophils, and eosinophils) (4–6). AIT is the only available specific approach for the treatment of allergies with long-term clinical benefits (symptoms remission and prevention of new sensitizations for several years after discontinuation) (5–7). The route of administration depends on allergenic extract availability and patient's perspective (8).

If AIT is recommended in allergic rhinitis (AR), its use in patients with AA is still controversial (9). A limited number of studies were conducted with an acceptable methodology, including asthma symptoms with

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concomitant measurement of objective variables (such as lung function), and most of them in mild asthma (10). According to current guidelines, AIT is recommended only for patients with controlled asthma, children, and adults, whose symptoms are clearly linked to a relevant allergen (11).

The purpose of this article is to review the published data on the impact of AIT (with the most common allergen extracts) on AA outcomes, including both clinical parameters and patients' subjective experience [quality of life (QoL)].

Data sources

This review examines the literature linking AIT with certain allergen extracts to asthma across several databases, including PubMed, Scopus, Web of Science between 2002 and 2019. The following key terms were used: "allergen immunotherapy" and "asthma" in combination with "house dust mite," "birch pollen," "grass pollen," "olive tree pollen," "molds," "pets," and "asthma quality of life." Randomized controlled trials (RCTs) and meta-analysis from reviewed publications were included. The impact of the immunotherapy was discussed separately for the most common aero-allergens. Results were limited to publications in English and Spanish languages. Preference was given to recent articles.

Results and discussion

Impact of AIT on asthma outcomes

House dust mite immunotherapy

The house dust mite (HDM) is a major source of indoor allergens and the most common allergen associated with asthma (12). People with HDM sensitization have recurrent exacerbations, impaired lung function, and increased asthma severity. This allergy is a potential target for AIT (13). HDM AIT is currently administered in AA via SCIT or SLIT, the latter with two alternatives: drops and tablets (10). Several asthma guidelines include HDM AIT as an effective treatment option for selected adults and children with AA and in patients with AR associated with AA (1,9).

A recent comprehensive meta-analysis including 19 RCTs with 796 participants (adults and children) with FEV1 > 70% of predicted values (14) evaluated the effect of SCIT on HDM-induced AA and suggested that SCIT administrated for at least 4 months was helpful in alleviating symptoms and in reducing medication compared with controls, without an improvement in lung function. The authors confirmed the acceptable safety profile of SCIT (14,15). Another meta-analysis including 42 HDM-SCIT RCTs (with significant heterogeneity) showed that SCIT reduced asthma symptoms, medications, and improved airway hyperreactivity (AHR) (16).

More recently, a systematic review including 51 trials which evaluated HDM AIT (SCIT and SLIT) in children and in adults found that AIT for HDM-induced AA can achieve substantial reduction in short-term symptom and medication scores without significant adverse reactions. However, more data are needed in relation to long-term effectiveness (17).

Some large clinical trials specifically designed for HDM-induced AA were performed using SLIT with tablets and all confirmed an improvement of asthma symptoms, a decrease in number of exacerbations, and a significant reduction in the use of inhaled corticosteroids (ICS) dose required to maintain asthma control (10,18). In the study by Virchow et al. (19), two different doses (6 SQ-HDM and 12 SQ-HDM) of the SQ-HDM SLIT tablet were compared in adults with HDM-induced AA treated by ICS. The addition of SLIT to maintenance medications improved time to first moderate or severe asthma exacerbation during an ICS reduction period compared with placebo. The treatment was well-tolerated with a favorable safety profile even in patients whose symptoms were not well controlled at randomization (19) and the tolerability was satisfactory (20). Currently, in some European countries, 12 SQ-HDM SLIT tablet represents the only available treatment for adults with HDM-induced AA associated with mild-to-severe HDM-AR.

The potential benefit of SCIT and SLIT in enabling successful step down of the ICS dose in GINA step 3 or 4 was evaluated by Demoly et al. (21). The authors concluded that individuals with moderate rather than mild HDM-induced AA are the patients who are more likely to benefit from the addition of AIT to their controller asthma treatment. A limited number of studies suggest that even HDM SLIT drops can be effective in HDM-induced allergy (22).

Although SCIT is widely considered safe and well tolerated, there is potential for serious systemic reactions, particularly in patients with uncontrolled asthma. Most of fatal reactions in the past occurred in this population at the time of the injection. No fatal reactions have been reported from SLIT. The lower frequency and severity of systemic reactions allow SLIT to be home administered after the first dose (23).

Limited evidences on the cost-effectiveness of HDM AIT are available. A study assessing HDM SCIT in children and adolescents with HDM-induced AA found it to be cost-effective 4 years after treatment

suspension compared with children receiving only the conventional therapy for asthma (24). A recent cost analysis study showed that the SQ-HDM SLIT tablet plus standard pharmacotherapy is cost-effective compared with placebo plus pharmacotherapy for HDM AA patients (25).

Pollen immunotherapy

The prevalence of sensitization to pollens is high. Almost 30% of Europeans are sensitized to Timothy grass and grass mixture pollen and 21% to birch pollen. Olive tree pollen is also an important cause of respiratory allergy in Mediterranean countries (26). The link between hay fever and asthma is now recognized because 20% of all hay fever patients develop asthma later in life. If one-half of patients with pollen allergy have AHR outside of the pollen season, the prevalence is increased to 73% of patients during the season (27). Pollen-induced seasonal AA is one of the most common phenotypes of asthma and a target of AIT (5).

Results from recent studies showed that in birch pollen–allergic patients with mild-to-moderate asthma, AIT could reduce AHR and was effective in reducing seasonal asthma worsening in Japanese cedar pollinosis (28).

An observational prospective trial evaluated the efficacy of a consecutive 2-year SLIT on severity of symptoms in patients suffering from respiratory allergies (rhino-conjunctivitis and/or mild-to-moderate asthma) due to grass or tree pollens, including olive. The authors concluded that a 2-year SLIT administration induced a significant reduction in asthma symptom score compared with baseline with a good safety and tolerability profile (29). A systematic review on the effectiveness and safety of AIT for AA published recently, provided evidence for a significant improvement in short-term symptom score after treatment with grass pollen AIT and suggested, but did not confirm, benefit from tree pollen AIT. The same review demonstrated a benefit of AIT with tree pollen on medication score and suggested, but not confirmed, a benefit for grass pollen (17).

According to the European Academy of Allergy and Clinical Immunology (EAACI) recommendations, AIT is the only way to effectively control allergy symptoms and to change the natural courses of allergy from AR to AA (30). The PAT study showed that a 3-year course of grass or birch pollen SCIT had long-term clinical effects and potentially prevented the development of asthma for up to 7 years after treatment cessation (27). More recently, data from the GAP study in children with grass pollen allergy indicated that SQ grass SLIT tablet reduced the risk of experiencing asthma symptoms and using asthma medication, this lasted for two documented post-treatment years. There was no difference in time to onset of asthma between active and placebo groups. The number of children with AR needed to be treated to prevent one case of asthma ranged in the GAP study from 10 to 13 with a trend for a smaller number in the youngest age group (31).

Results from recent studies strengthen the evidence for real-world benefits of birch and grass pollen AIT by a reduction of the risk of new asthma onset, slower asthma progression, and decrease of asthma medication intake (32,33).

The potential of grass pollen SLIT to protect thunderstorm asthma in patients with seasonal AR was evaluated in an open-label study. Clinical benefit was demonstrated with a 4-month per seasonal regimen of five-grass SLIT tablet. The addition of grass SLIT tablet to standard pharmacotherapy reduced significantly the asthma exacerbation rate in patients with seasonal AR exposed to the thunderstorm (0% vs. 41%, $p < 0.005$) (34).

Recognized risk factors for fatal reactions in SCIT include uncontrolled asthma at the time of administration, dosing errors, delay or inadequate administration of epinephrine during anaphylaxis, a prior history of injection-related systemic reactions, and administration of injections during peak allergy seasons. SLIT has a more favorable safety profile than SCIT. When considering severe systemic reactions, patients receiving SLIT appear to be at considerably lower risk than patients receiving SCIT. SLIT also appears to present no greater risk for adverse reactions in well-controlled asthmatic patients (23).

Mold immunotherapy

Fungi are organisms that live as saprophytes, parasites, or symbionts in their plant or animal host, which grow in intra- and extra-domiciliary environments. Among over 100,000 fungal species reported, about 80 mold genera have been shown to induce allergies in susceptible individuals. *Penicillium, Aspergillus, Cladosporium,* and *Alternaria* are reportedly the most prevalent fungal aero-allergens worldwide (35). Spores from the former two genera are present all year round, whereas *Cladosporium* and *Alternaria* tend to show seasonal peaks, primarily during the rainy season from April to October (36). Although the prevalence of sensitization to fungi is not precisely known, it can reach 50% in inner cities and has been

identified as a risk factor in the development of asthma, both in children and adults (37,38).

Alternaria is the only mold allergen where medical documentation confirms a significant benefit in AA after AIT in controlled studies including children and adults (39). It is known that the effectiveness is dependent upon the quality of the product. Development of methods for extraction and assessment of the main allergen, *Alt a1*, occurred because standardization made it possible to extract *Alternaria alternata*. Studies that used a product containing the standardized *Alternaria alternata* extract confirmed its effectiveness. This treatment led to reduced asthma symptoms and medication, decreased serum-specific IgE levels, and increased serum-specific IgG4 levels to *Alternaria* (39).

A randomized, double-blind, placebo-controlled study evaluated the safety of SCIT with *Alternaria alternata* standard extract in patients with AR with or without mild-to-moderate AA and showed a decrease in the combined symptoms/medication index and cutaneous reactivity with increase of IgG4-allergen induced level. The most effective and safest dose was 0.36 mg of *Alt a1* is given monthly for 2 years (40).

In contrast, less evidence exist on the effectiveness of AIT with *Cladosporium* in AA. The major problem is the lack of a standardized extract, so no recommendation exists for this therapy by international consensus. Similarly, only case reports or uncontrolled studies are available regarding AITs for *Candida albicans* or *Aspergillus fumigatus* in AA, not sufficient for their recommendation in practice (39).

Di Bona et al. performed a systematic review of efficacy and safety of AIT for the treatment of respiratory allergies to molds. The primary outcomes were the symptoms and the medication scores, as well as the safety of this treatment in patients receiving AIT compared with controls. They included randomized studies comparing AIT (SCIT and SLIT) with the placebo/controller therapy. A total of 9 studies (168 children, 99 adults; median sample size 27) met inclusion criteria with a risk of bias moderate-to-high. Low evidence supports the assumption that AIT with *Cladosporium herbarum* or *Alternaria alternata/ Alternaria tenius* are effective in reducing symptoms and medication use, with only four out of nine studies reporting higher benefit of AIT versus comparators. The highest benefit of AIT compared with placebo was found on medication score in studies with a longer follow-up and low-risk of bias. No difference was reported with respect to study sample size, route of administration, and age of participants. Generalized adverse reactions were reported in 12.5% of the participants treated with SLIT, and 37.2% of the participants treated with SCIT. The authors concluded that low strength evidence suggests that mold AIT is efficacious for the treatment of respiratory allergies. High-quality studies with an adequate sample size are needed (41).

Recently, a new *Alternaria alternata* allergoid had been produced and showed a good efficacy leading to cytokine stimulation and inducing synthesis of IgG4 antibodies able to block IgE binding to the allergen. In addition, no toxic effect was observed, and the synthesized product has a similar safety profile as the native extract (42).

Pet immunotherapy

People easily come in contact with pet allergens, as pet ownership is very common. Sensitization to animal allergens can result from housing conditions or occupational settings. Importantly, exposure to pet allergens does not require a direct contact with the animals. These allergens are widely present in homes without pets at levels able to sensitize and cause symptoms (43). Cats and dogs are among the most common sources of aero-allergens. When measuring the prevalence of skin prick test positivity, it was established that sensitization to cats or dogs was around 20% in adults below 45 years and around 13% in adults over 45 years in many parts of Europe (26). Polysensitization to animal dander is not rare. In some areas, the frequency of asthmatic children sensitized to domestic pets has been reported to be up to 50–70% (44). Although allergen avoidance measures may help, patients often oppose removing pets from their environment, or it is insufficient to achieve complete allergen isolation. However, a routine pet avoidance is not recommended to infants and preschool children for reducing the risk of developing allergy or asthma (45).

Current information on AIT in pet allergy and asthma suggests that it can be effective in reducing allergic symptoms. Clinical efficacy of cat SLIT in patients with rhino-conjunctivitis with or without AA based on natural exposure challenge test was assessed in a double-blind, placebo-controlled study (46). A marked reduction in symptoms was shown in the active group with a reduced peak expiratory flow response to cat exposure and an improvement in skin test reactivity to a standardized cat extract without significant changes in the placebo group.

Abramson et al. performed a systematic review of SCIT studies in asthma due to sensitization to cats

and dogs (16). It was demonstrated that asthma symptom scores were improved in two of three studies, whereas there was a tendency for another one. Only one study analyzed lung function parameters and tended to show a favorable effect of SCIT. Two studies demonstrated a statistically significant favorable effect on the nonspecific AHR, and another one on allergen-specific AHR. The risk ratios for systemic reactions varied from 1.20 to 3.56 (16). A recent systematic review found an improvement of short-term symptom score by the AIT with cat/dog dander (17).

Based on the current results, AIT for pet allergies has the potential for being a treatment of choice for asthma patients. However, the number of studies is very low and additional high-quality RCTs are needed.

Impact of AIT on QoL in asthma population

The assessment of Health-Related Quality of Life (HRQoL) has been implemented as a key outcome in clinical research on asthma (47). This multidimensional construct refers to the impact of both illness and treatment upon the patient as perceived by the patient himself. The availability of validated tools allowed the evaluation of the impact of the disease and treatment from the patient's perspective and the integration of the objective assessment of asthma with subjective perceptions (48).

HRQoL has been evaluated as secondary outcome in several RCTs which studied the effect of AIT in patients with AA. A systematic review of the EAACI on the effectiveness and safety of AIT for AA evaluated the studies published up to 2015. Out of 98 selected trials, 11 studies evaluated HRQoL as a secondary outcome by comparing active and placebo groups. A significant improvement in HRQoL after treatment with SCIT was found in adult patients sensitized to *Dermatophagoides sp.* and children/adolescents who were allergic to *Alternaria alternata* (17).

The available results for SLIT appear more controversial. If two studies including adults and children demonstrated evidence of improved QoL related to asthma by AIT with *Dermatophagoides sp.* (49,50), no difference was found between active and placebo group in RCT that involved adult patients (20,51–53) or in the group of adolescents enrolled in the study of Pham (50).

The analysis of the recent literature shows that minimal data on the impact of immunotherapy on QoL related to asthma are available. Some studies that include AR patients with or without comorbid asthma only use a HRQoL questionnaire for rhinitis, not for asthma (53–56).

A recent study assessed the efficacy and safety of a 2-year SCIT treatment in 58 HDM allergic patients. HRQoL was assessed as the secondary outcome by means of Rhino-conjunctivitis Quality of Life Questionnaire (RQLQ) and the Asthma Quality of Life Questionnaire (AQLQ) (57). During the treatment period, despite RQLQ scores remaining unsatisfactory, a significant improvement of AQLQ was detected in patients with comorbid asthma (51–57). In this subgroup, the achievement of near maximal AQLQ scores suggests that impact of asthma on daily life is minimal or absent.

A real-life study aimed to investigate the adherence with grass pollen SLIT tablet and QoL related to both rhinitis and asthma in a sample of 236 adults and 163 children. In the overall population of adult patients, mini-RQLQ scores significantly improved during the 3 years of treatment. In patients with "comorbid asthma" (32.6%), an improvement of mini-AQLQ was detected when comparing baseline with the first grass pollen season, but not for the second and third ones. In a pediatric population, as detected by a generic questionnaire for allergic disease (Pediatric Allergic Disease quality of Life Questionnaire), HRQoL was significantly improved during the treatment period. The increase exceeded the minimal important difference threshold and thus was clinically significant (58).

Filanowicz et al. evaluated HRQoL as the primary outcome in 101 with AA and 99 with AR before and after completing a 3-year period of AIT (59). An average increase in QoL after treatment was detected in both groups, although it was lower in AA than in AR (0.84 vs. 1.50). It was concluded that AIT, from the point of view of the improvement of QoL, was a valuable therapeutic tool in patients with AA and AR.

Conclusion

Three quarters of asthmatic patients are sensitized to at last one aero-allergen and persistent exposure is associated with poorer asthma outcomes. The only treatment that could potentially change the course of the allergic disease is AIT. Both methods of AIT (SCIT and SLIT) are validated as efficient and safe but the risk of anaphylaxis is lower for the latter. Emerging data about the positive impact on asthma outcomes of AIT in patients with allergic airway disease allowed for the addition of this treatment in mild-to-moderate AA. The possible therapeutic role of AIT in severe AA remains a challenge and must be

defined in the future. While more evidence showed the effectiveness of HDM and pollens specific immunotherapy on asthma symptoms and medication use, limited data are available for the asthmatic patients sensitized to molds and pets. Several studies suggested an improvement in the QoL in asthmatics treated by AIT, but not all. Further research is needed on long-term and cost-effectiveness of AIT in asthma population, the impact on the QoL and its possible place in severe asthma therapeutics.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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