Literature Review

Efficacy and Safety of Allergen Immunotherapy to Treat House Dust Mite Allergic Asthma in Children.

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160 Character summary of article: This article compares the efficacy and safety of subcutaneous and sublingual immunotherapy in the treatment of allergic asthma triggered by house dust mite.

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Abstract

Allergic asthma is a significant disease of childhood, of which, house dust mite is the most common trigger. There have been many investigations into the role of allergen immunotherapy in preventing the development of allergic asthma, and potentially its treatment following formal diagnosis, as evidenced by studies demonstrating significant improvements in medication use, asthma symptoms, and respiratory function. However, there is a paucity of research into specific populations – significantly, paediatric populations. This article reviews the recent literature regarding the efficacy and safety of allergen immunotherapy in the treatment of house dust mite-allergic asthma, with a focus on paediatric populations.

This review suggests that immunotherapy effectively improves asthma symptoms and severity in paediatric populations. While adverse reactions may occur, serious or life-threatening reactions are rare. More research is required to investigate immunotherapy in populations who are polysensitised or who have severe or uncontrolled asthma – preliminary evidence suggests immunotherapy may have a role in the treatment of these patients.

Key Points

1. House dust mite is the most common trigger in allergic asthma, and is near to ubiquitously present in day to day life.
2. Subcutaneous and sublingual immunotherapies have demonstrated efficacy in the treatment of these patients, and safety data demonstrates that serious or life-threatening allergic reactions are rare.
3. Allergen immunotherapy should be seriously considered in the management of the asthmatic child with house dust mite-allergic disease.

Introduction

Asthma is a condition affecting people of all ages that is increasing in prevalence. Approximately 50% of asthmatics have a significant allergic basis to their disease development, with up to 95% exhibiting a positive skin prick test to one or more allergens [1]. Allergic asthma (AA) is most commonly identified in people allergic to house dust mite (HDM), specifically *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* [2]. Asthmatics sensitised to HDM have lower FEV1 and FEV1/FVC ratios on lung function testing than non-sensitised asthmatics [3]. AA often develops as part of the atopic march in children, along with allergic rhinitis, allergic conjunctivitis and atopic dermatitis [1-3]. Current first-line management of asthma involves medications that reduce smooth muscle constriction and airway inflammation, alongside allergen avoidance [1]. However, unlike allergen immunotherapy (AIT), these treatments do not alter the natural history of the disease [4].

The appeal of AIT lies in its potential to induce tolerance through repeated exposure to increasing doses of an allergen, with a "build-up phase" and a "maintenance phase [1]". AIT produces significant immunological changes, including increased specific IgG and, to a lesser extent, decreased specific IgE [5-9]. Originally, allergens were administered via subcutaneous immunotherapy (SCIT) injections, with subsequent development of sublingual immunotherapy (SLIT) liquids and tablets. SCIT is delivered in a controlled clinical setting, while SLIT can be delivered in the patient's home without clinical supervision and offers appealing ease of administration in paediatric populations. Current evidence suggests that SLIT is safer than SCIT, although they appear to be equally effective [4,10,11], but most literature examines adult populations. This review aims to evaluate the current efficacy and safety evidence of SCIT and SLIT in the treatment of paediatric HDM-AA.

Efficacy of house dust mite immunotherapy to treat asthma

The efficacy of HDM immunotherapy, both SCIT and SLIT, in treating AA has been validated. Three years of immunotherapy is effective in improving asthma symptoms, asthma-free rates, validated questionnaire scores, and medication use [6,11-15], with the literature demonstrating that the efficacy of SCIT and SLIT are comparable. SCIT has additionally been shown to significantly decrease the likelihood of developing additional sensitisations [16]. Longer duration of immunotherapy is not associated with improved outcomes [12,17] and shorter duration of immunotherapy tends to observe fewer or non-significant improvements [5,7,18-21]. Unless stated otherwise, all papers referenced studied monoallergenic HDM-AIT in HDM-allergic populations not controlled for polysensitivity. The efficacy of SCIT and SLIT is compared in Table 1.

Paediatric investigations into SCIT

Arroabarren *et al.* [12] investigated 71 children and reported that three years of SCIT significantly decreased asthma symptom score, medication score, and global symptom and medication score compared to baseline. Sixty nine percent of asthmatic participants were reported as asthma-free with normal lung function testing and pharmacology-free for three months [12]. These findings are supported by a study of 90 children [6], which demonstrated that, compared to placebo, three years of SCIT resulted in a significantly decreased inhaled corticosteroids (ICS) dose, significantly higher ICS cessation rate, significantly lower asthma symptom scores and significantly increased peak expiratory flow (PEF). Another study of 31 children [11,13] confirmed that three years of SCIT significantly improved their visual analogue scale score by 63%, significantly decreased their total asthma symptom score by 86% and significantly decreased their total medication score by 82%.

Paediatric investigations into SLIT

Ozdemir *et al.* [15] demonstrated that in 90 children, three years of SLIT significantly decreased the number of months per year requiring ICS, the mean daily dose of ICS and the ICS cessation rate, but longer than three years of SLIT show no significant difference in respiratory outcomes. Trebuchon *et al.* [14] retrospectively analysed 736 children, in whom the median duration of SLIT treatment was 3.1 years. Although there was no control group, physicians perceived SLIT to be efficacious in 83% of participants, and asthma symptoms to have improved in 64%. Compared to baseline, there were trends of reductions in medication use, including oral antihistamines, ICS, long-acting beta-agonists and short-acting beta-agonists. Eifan *et al.* [13] and Karakoc-Aydiner *et al.* [11] demonstrated three years of SLIT significantly improved asthma and medication scores compared to control; however, there were no differences in lung function. De Bot *et al.* [22] found two years of SLIT in children lowered dyspnoea/wheeze score compared to placebo, but there was no difference for dry cough score.

Adult investigations into SCIT and SLIT

Studies in both adult and limited paediatric populations have found that three years of AIT is efficacious and that a shorter duration of therapy tends to have fewer significant outcomes [8,17,19-21,23]. Tabar *et al.* [17] reported on a mixed paediatric/adult population, randomised to three or five years of SCIT, and reported that three years of SCIT significantly improved asthma symptoms and asthma-free rates. Blumberga *et al.* [8,23] reported on 42 adults and show that, compared to control, three years of SCIT significantly improved HDM tolerance and decreased inflammatory responses. Potter *et al.* [21] reported on two years of SLIT in 48 adults and found no significant differences compared to placebo for ICS use and clinical outcomes. A study of one year of SLIT in 604 adults [19,20] demonstrated improvements in daily ICS use and ICS cessation rate compared to

placebo. There were no statistical differences for any asthma parameters. Virchow *et al.* [7] reported on six months of SLIT in 834 adults, finding a significantly reduced risk of moderate or severe asthma exacerbation compared to placebo, but no significant difference in questionnaire scores.

Efficacy of SCIT and SLIT

Although three years of immunotherapy, whether SCIT or SLIT, has proven efficacious in reducing medication use and improving asthma symptoms, there is still marked variability in outcomes even within the same duration of treatment. Studies clarifying optimal dosing and administration, particularly in paediatric populations, may reinforce whether or not there is a role for SCIT and/or SLIT in treating HDM-AA in children.

Safety of house dust mite immunotherapy to treat asthma

Inherent in AIT is the potential to induce local or systemic adverse reactions [1,24,25]. The World Allergy Organisation (WAO) has standardised reporting of SCIT- and SLIT-related adverse reactions [25]. Local SCIT reactions include erythema, pruritus and injection site swelling, while local SLIT reactions include mouth/ear, upper gastrointestinal, and lower gastrointestinal reactions. The spectrum of systemic reactions ranges from mild rhinitis to cardiac arrest and anaphylaxis. SLIT is widely considered to be safer than SCIT, with fewer adverse reactions and no deaths reported to date [1,10,26]. The safety of SCIT and SLIT is compared in Table 2.

Local reactions to immunotherapy

Local reactions to SCIT are not uncommon, though the size of a local reaction is not standardised in the literature [6,12,18,27]. Nacaroglu *et al.* [27] found that HDM-SCIT was significantly more likely to precipitate a wide local reaction (>5cm) compared to grass, olive, or weed pollen SCIT. The reported rates of injections producing local reactions range from one per nine doses [6] to one per 260 doses [27]. Local reactions generally resolve spontaneously, though oral antihistamines can be used to good effect [12]. It is generally accepted that SLIT produces more local than systemic reactions [1,14,15,28] and that these predominantly consist of oral itching or taste sensation.

Systemic reactions to immunotherapy

The most common systemic reaction reported in SCIT and SLIT are asthma symptoms [11-13,16,27]. Other reported systemic effects include fatigue [16], dizziness [19], migraine [19], arthralgia [7], rhinorrhoea [15] and sneezing [15].

The reported rates of SCIT-related systemic reactions vary from one reaction per 300 doses [29] to one per 3,300 doses [12]. The rate of near-death reactions has been reported at one in a million and the rate of death due to SCIT has previously been reported at one per 2.5 million doses [9] – no deaths due to SCIT have been reported since 2009, when a 43 year old male developed airway obstruction and cardiopulmonary arrest [30,31]. Uncontrolled asthma has been identified as an important risk factor for fatal and near-fatal reactions in HDM-SCIT [31].

Severe reactions are rare in SLIT, with a reported rate of one severe reaction per 384 treatment years, and no life-threatening reactions reported to date [1,28,32]. Two recent paediatric case reports detail two cases of severe reactions to HDM-SLIT. Galip and Bahceciler [33] reported on a five year old boy with HDM-allergic rhinitis who, during the up-dosing phase of SLIT, began vomiting intractably after five minutes of administration. The boy remained nauseated for 40

minutes. This occurred whenever the particular dose was administered. Blazowski [34] reported on a sixteen year old girl with HDM-AR and HDM-AA who, in her third year of maintenance SLIT, self-ceased her usual dose of 10 drops daily for three weeks, then self-administered 60 drops. This induced a severe systemic anaphylactic reaction, which required ICU support. These two reports demonstrate that severe systemic reactions to SLIT are possible, but that much of the risk of harm can be mitigated by observing the patient following SLIT administration.

Further high-quality studies in both paediatric and adult populations have already been called for [1,10,24], and would help to define the safety of SLIT in the treatment of HDM-AA in children.

SCIT vs. SLIT in the paediatric patient

Due to the scarcity of studies specifically investigating paediatric patients, it is difficult to draw strong conclusions. Using what data is available (Table 1), it can be seen that SLIT, whilst significantly effective in its own right, may be less efficacious than SCIT. Further statistical testing to assess this question in this review is not possible as the raw data from these investigations are not available.

Separate from the question of whether SCIT or SLIT is more effective in a head to head comparison is the question of practicality and ease of administration for patients. Following the first observed dose of SLIT, all subsequent doses can be self-administered at home [35] – this option is not available for SCIT. The increased safety profile of SLIT may also be more attractive to the parents of these patients. As reviewed earlier in two case studies [33,34]; however, SLIT does inherently have a risk of adverse reaction and should these complications arise in the home rather than the hospital, appropriate staff and treatment may not be close to hand. For these reasons, it is imperative to discuss with patients and their parents the risks and benefits to each of SLIT and SCIT and ensure they are well informed prior to starting any treatment.

HDM-AIT in polysensitised patients

Up to 30-80% of allergic patients worldwide are polysensitised [36]. There is concern regarding the safety and efficacy of single- or multiple-allergen immunotherapy in polysensitised patients, with a small number of recent studies addressing this. Nacaroglu *et al.* [27] retrospectively evaluated adverse reactions to single-allergen or multiple-allergen SCIT in children, 48.9% of whom were sensitised to HDM. They found that adverse reactions were significantly more common in patients undergoing polyallergenic SCIT compared to monoallergenic SCIT, and in HDM-SCIT compared to SCIT with grass, olive, or weed pollens; animal dander; or *Alternaria* fungi. There was no statistically significant difference in adverse reactions between monosensitised or polysensitised participants. Nelson [37] reviewed 13 studies utilising polyallergenic AIT and identified that simultaneous administration of multiple allergens is clinically effective, but called for more studies to draw stronger conclusions – a position recognised by a 2014 international consensus paper [38], which noted that virtually all published RCTs are of single-allergen AIT, but acknowledged that the evidence so far indicates that AIT is equally effective in monosensitised and polysensitised patients. Of note, while many RCTs of AIT do not exclude polysensitised participants, it is difficult to draw conclusions from these papers as results are typically not analysed or reported separately. Interestingly, it has been demonstrated that immunotherapy in monosensitised children can reduce the rate of development of subsequent polysensitivity [16].

House dust mite immunotherapy in poorly-controlled or moderate-severe asthma

The use of AIT in varying severity of disease has been heavily debated, guided by the risk of adverse reactions. The risk of allergic reaction suggests AIT may be better suited for mild AA, with a lower risk of anaphylaxis [39], while the risk of anaphylaxis implies AIT should be a final-line therapy in uncontrolled severe AA – the position of many governing bodies [38]. A number of studies have investigated the safety and efficacy of AIT in moderate to severe asthma [7,19,23,40].

Gonzalez *et al.* [40] investigated SCIT in eight adults with severe persistent HDM-AA and observed few minor local reactions, no significant reactions and no late reactions. Blumberga *et al.* [23] reported on SCIT in 42 adults with moderate to severe HDM-AA, finding mixed efficacy, but generally safe outcomes: 38% of SCIT participants developed mild systemic or non-life-threatening reactions, one severe local reaction was treated with oral ICS and nebulised β2-agonists and there were no life-threatening reactions.

De Blay *et al.* [19] analysed SLIT in 604 adults. They found that medication and symptom scores were significantly more improved in patients with partly-controlled asthma compared to patients with non-severe asthma. While there was a dose-dependent increase in adverse reactions, the majority were mild or moderate. Virchow *et al.* [7] reported comprehensive safety data of SLIT in 834 adults with partly-controlled asthma. Of participants, 30.6% experienced adverse reactions compared to 3.4% of non-SLIT participants: 74.1% of these were local reactions and while 3% were considered severe, none compromised the airway. There were no severe or life-threatening systemic reactions.

Uncontrolled asthma is an important risk factor in the development of adverse reactions to AIT [31]. The literature demonstrates that AIT in poorly-controlled or severe asthma enacts similar or greater efficacy than in mild asthma, without a significantly higher risk of severe adverse reactions – a position that is at odds with current guidelines.

Current guidelines for immunotherapy to treat allergic asthma

Many guidelines exist to direct AIT in the management of AA, with most recommending a cautious approach. The 2016 Australasian Society of Clinical Immunology and Allergy recommends that AIT can be considered based on clinical judgement when symptoms are severe, the allergen is difficult to avoid and medications are ineffective or intolerable.

Future directions for allergen immunotherapy

In addition to ongoing trials to clarify the efficacy and safety of SCIT and SLIT, there is ongoing research into adjuvants to increase tolerability and into alternative immunotherapy methods [35]. Adjuvants such as toll-like receptor 4 and 9 agonists increase Th1 and Treg responses, though clinical trials have shown inconsistent efficacy. Depots of allergens with a second immunogenic material such as alum or calcium phosphate have been used in Europe, though further assessment is needed before more widespread use. Alternative delivery methods, including epicutaneous and intralymphatic methods are also being investigated, though to date no studies for HDM-AR or AA have been performed. Further investigations into alternate hypoallergenic allergens and the co-administration of monoclonal antibodies with the allergen are also underway. As these studies progress, more information about the various options, efficacy, and safety of immunotherapy will become apparent.

Conclusion

Allergen immunotherapy has the potential to change the natural history of allergic asthma [4] and as such, should be considered in the management of patients with AA. The literature suggests that AIT is superior to placebo in improving asthma symptoms, asthma-free rates, and medication use [6,11-15]. Adverse reaction rates vary between SCIT and SLIT, but serious or life-threatening reactions are rare [1,12,28,29,32], with no SLIT-related death reported [10] and no SCIT-related death since 2009 [30,31]. Ongoing concerns regarding safety remain, and the superiority of SCIT or SLIT has not been ascertained. More research is required to investigate AIT in the polysensitised and severe or uncontrolled asthma populations, with current evidence suggestive of a role for both SLIT and SCIT in these patients.

The current lack of high-powered well-designed studies in specific populations such as paediatric, HDM-AA, or severe asthma, renders analysis by systematic review or meta-analysis problematic. Further studies into the efficacy and safety of HDM-AIT in these specific populations will make the role of treatment clearer. AIT can facilitate a significantly improved quality of life in the appropriate patient: our role as clinicians will be to identify these patients.

Conflicts of Interest

There are no conflicts of interest to declare.

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Tables

Table 1: Comparison of efficacy of subcutaneous immunotherapy and sublingual immunotherapy. *Referenced papers studied three years of monoallergenic house dust mite (HDM) immunotherapy in HDM-allergic populations not controlled for polysensitivity.*

Parameter	Subcutaneous immunotherapy (SCIT)	Sublingual immunotherapy (SLIT)
Significantly decreased asthma symptom score, compared to baseline	70-100% of participants [12] 63-86% improvement [11,13,17] −1.4 to 2.1 points (four-point scale) [6]	64-83% of participants [14] 44-86% improvement [11,13]
Significantly improved medication scores (undefined), compared to baseline	100% of participants [12] 82% improvement (undefined scale) [11,13]	Trends of improvement [14] 64% improvement (undefined scale) [11,13]
Significantly decreased inhaled corticosteroid use, compared to baseline	− 125.4 µg [6]	Decreased requirement from 12 to 7 months per year [15] − 120 µg [15]
Significantly higher inhaled corticosteroid cessation rate compared to control	28.9% [6]	52% [15]
Significantly increased peak expiratory flow, compared to baseline	+ 28 L/min [6]	No significant results
Asthma-free rates compared to baseline	62.7-74.6% [12,17]	No significant results
Other	Significantly decreased likelihood of developing additional sensitisations [16]	–
Papers that studied fewer than three years of immunotherapy	Observed fewer, or non-significant, improvements in clinical and medication outcomes [5,18]	Observed fewer, or non-significant, improvements in clinical and medication outcomes [7,19-21]

Table 2: Comparison of safety of subcutaneous immunotherapy and sublingual immunotherapy. *Referenced papers studied three years of monoallergenic house dust mite (HDM) immunotherapy in HDM-allergic populations not controlled for polysensitivity.*

Adverse reaction	Subcutaneous immunotherapy (SCIT)	Sublingual immunotherapy (SLIT)
Local Reactions		
Local skin / oral reaction	Occurred, not quantified [11,13,16,18] 0.38-11.6% of doses [6,17,27,29] 11.9% of participants [29]	3.3-15.9% of participants [14,15] "Common", not quantified [19,21]
Other oral reaction	–	One case – moderate laryngeal oedema, did not compromise airway [7]
Systemic Reactions		
Unspecified	0.06-4.7% of doses [6,8,23,27,29] 3.7-24% of participants [8,23,29]	3.1% of participants [14]
Fatigue	"Common", not quantified [16]	–
Dizziness / migraine	–	1.9% of participants [19]
Arthralgia	–	0.1% of participants [7]
Rhinorrhoea / sneezing	–	1.1% of participants [15]
Asthma / shortness of breath	0.035-0.067% of doses [12,17,27] 2.4-6.5% of participants [11,13,16,27]	0.1% of participants [7]
Anaphylactoid / anaphylaxis (not fatal)	0.8% of participants [16]	One case (see text) [34]
Death	One per 2.5 million doses [9]	Nil reported to date