

Which patients with asthma are most likely to benefit from allergen immunotherapy?



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If allergen immunotherapy (AIT) is to be considered as a treatment option for allergic asthma, it must undergo the same developmental steps as other antiasthmatic drugs. The bronchial allergen challenge model has demonstrated excellent negative predictive value for the development of new therapies for asthma. Subcutaneous immunotherapy appears to have a clinical and significant effect on the early asthmatic response to mite, cat, and birch and grass pollens in children and adults. Use of AIT in children with asthma is widely practiced but not supported by as strong a level of evidence as in adults. House dust mite sublingual immunotherapy tablets demonstrate efficacy in asthma exacerbations and other outcomes when used

as add-on therapy in adult patients. Using a biologic to improve the patient's lung functions and asthma control before initiating AIT can transform unsuitable candidates for AIT into appropriate candidates. Because AIT is a form of personalized medicine, phenotyping the most suitable patient is necessary. Field studies of adults and children have suggested that polysensitized patients with rhinitis and Global Initiative for Asthma class 2 to class 4 asthma appear the most likely to be good responders. We hypothesized that AIT responders are those who demonstrate a high eosinophilic response to natural or experimental exposure. (*J Allergy Clin Immunol* 2022;149:833-43.)

Key words: Allergic asthma, allergen immunotherapy, airway inflammation, biologics, eosinophils, bronchial hyperresponsiveness

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The efficacy of allergenic immunotherapy (AIT) in asthma has recently been recognized and still recommended in the Global Initiative for Asthma (GINA) guidelines.¹ Since AIT was first recommended, its efficacy has been endorsed only in patients with allergic rhinitis (AR) and/or conjunctivitis. In contrast, its use in asthma has been one of the most debated aspects in the field for several decades.^{2,3} Another aspect of this debate is concern over safety and risks of anaphylaxis in patients with asthma, particularly in patients undergoing subcutaneous immunotherapy (SCIT).² If AIT is to be considered as a treatment option for allergic asthma, it must undergo the same developmental steps as other antiasthmatic drugs. As stated by O'Byrne et al, the bronchial allergen challenge (BAC) model has demonstrated excellent negative predictive value for the development of new drugs for asthma.⁴⁻⁶ Indeed, there is no example of an approved antiasthmatic drug that did not demonstrate its efficacy in early asthmatic response (EAR) and/or late asthmatic response (LAR) when compared with placebo during an allergen exposure.⁴ However, the positive predictive value is moderate, as it is possible to observe drug efficacy during a BAC but not in a field study. This has been the case for some leukotriene inhibitors and anti-PAF-acether.⁴

In this article, we will first review the effects of AIT on asthma outcomes obtained in studies of nonspecific and specific bronchial hyperresponsiveness (BHR) in children and adults with allergic asthma, as well as the results of field studies with sublingual AIT in children and adult patients with asthma. In the second part of the review, we will discuss how AIT in patients with allergic asthma might be improved by adding biologics or by tailoring the AIT more specifically to the patient's phenotype.

Abbreviations used

AR:	Allergic rhinitis
AIT:	Allergenic immunotherapy
BAC:	Bronchial allergen challenge
BCT:	Bronchial allergen test
BHR:	Bronchial hyperresponsiveness
CCR4:	C-C chemokine receptor type 4
CRTH2:	Prostaglandin D ₂ receptor 2
DBPC:	Double-blind placebo-controlled
DR:	Dual response
DSS:	Daily symptom score
EAR:	Early asthmatic response
ECP:	Eosinophil cationic protein
FAS:	Full analysis set
FDA:	US Food and Drug Administration
HDM:	House dust mite
GINA:	Global Initiative for Asthma
ICS:	Inhaled corticosteroid
ILC2:	Group 2 innate lymphoid cell
LAR:	Late asthmatic response
MDC:	Macrophage-derived chemokine
NSBHR:	Nonspecific bronchial hyperresponsiveness
PD ₂₀ :	Provocative dose causing a 20% drop in FEV ₁ from baseline
PGE ₂ :	Prostaglandin E ₂
SBHR:	Specific bronchial hyperresponsiveness
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy
T2:	Type 2
TARC:	Thymus and activation-regulated chemokine

EFFECTS OF AIT ON NONSPECIFIC AND SPECIFIC BHR

Long-term AIT is thought to be associated with a significant reduction of nonspecific BHR (NSBHR) or specific BHR (SBHR) in both early (EAR) and late (LAR) allergen-induced responses (Table 1⁷⁻³²). The mechanism of LARs is thought to be different from the cell-mediated immediate reaction and to involve the recruitment, activation, and persistence of eosinophils and the activation of T cells following allergen exposure. Immunopathologic changes seen in the mucosal tissues of subjects chronically exposed to inhalant allergens resemble those seen during LARs. Because the LAR is associated with increased BHR and mimics pathologic inflammation, it has been postulated that the effect of AIT on LARs is relevant to its clinical efficacy.³³ Because the LAR alone is infrequent, consideration of the LAR includes the dual response (DR) of an EAR and a LAR.

MITE ALLERGY**Child patients**

Among children with asthma, 91% are dual responders.³⁴ It appears that having more severe asthma (requiring inhaled corticosteroids [ICSs]) and a mite-specific IgE titer of at least 19.6 kU/L predict a DR. However, baseline pulmonary function and the provocative dose of methacholine causing a 20% drop in FEV₁ from baseline (PD₂₀ methacholine) do not predict LARs.³⁴ The effects of AIT on EARs and LARs have been published in a few studies (Table 1). Van Bever et al performed 3 studies in children with asthma and mite allergy during 1 year of AIT to house dust mite (HDM).⁷⁻⁹ In the first 2 studies, they demonstrated a

reduction in EAR and LAR frequency and the severity of the LAR in the AIT group. In the third study, they found a significant effect on the provocative dose of HDM causing a 20% drop in FEV₁ from baseline (PD₂₀ HDM) but less than 1 doubling dose. No difference was found in NSBHR.⁸ These results were confirmed in another study of 30 children with asthma and mite allergy. A significant decrease in the bronchial LAR was found 4 months after desensitization had been achieved by using a polymerized extract of *Dermatophagoides pteronyssinus*, as was as an improvement in EAR, with a 12.8-fold increase in the provocative concentration of methacholine causing a 20% drop in FEV₁ from baseline.¹⁰

Adult patients

Several publications have shown that a DR occurs less frequently in adults with asthma and HDM allergy than in children with similar allergy. The frequency varies from 40% to 60%.³⁵⁻³⁷ The effect of AIT on bronchial response has been assessed in a few controlled studies (Table 1).^{13,15-18} All of the patients had mild-to-moderate asthma and rhinitis. BCTs (bronchial allergen tests) were performed after at least 1 year of SCIT using standard or modified allergen (allergoids). One study included patients with more severe (GINA class 4) allergy.¹⁸ In most of the studies, patients were under treatment with ICSs. In all of the studies, a significant increase in the mite allergen dose inducing a 20% drop in FEV₁ from baseline (ranging from 1.8- to 2-fold) was obtained. Only 1 publication has assessed the LAR.¹⁸ After 1 year, a significant decrease in DRs versus the rate in the sham group was obtained.¹⁸ A nonsignificant difference was found at years 2 and 3. Studies of NSBHR have all found a slight but significant improvement (ie, from 1 doubling dose to 2 doubling doses of the initially required dose).^{17,18} However, the results differed according to patient phenotype. In 1 study, the authors differentiated highly reactive (BHR < 100 µg) from less reactive patients (BHR > 100 µg). The highly reactive group appeared to have better improvement in BHR.¹⁸

OTHER ALLERGENS

DR are less frequent with cat allergen than with mite allergen.^{13,15,16,35-38} In a limited study, a 3-year course of SCIT given to children who had asthma along with cat and dog allergy and were under treatment with an ICS resulted in improvements (but not significant) in NSBHR and SBHR to cat and dog.²⁵ In adults, limited studies have demonstrated no significant effect of 1 to 2 years of SCIT on NSBHR, although they have demonstrated a significant increase in the cat allergen dose required to induce an EAR (1 doubling of the dose).²²⁻²⁴ Only 1 study has found a consistent and significant effect on bronchial sensitivity toward cat allergen and histamine. Cat allergen-treated patients were able to tolerate 11 times more allergen at the end of AIT.²¹

Adults with birch pollen allergy who had rhinitis and asthma (16 of 19 with a DR) were evaluated after 1 year of SCIT to birch pollen. An important improvement in the EAR was obtained with more than 3 doubling doses. An improvement in severity of the LAR was also obtained.²⁷ In children with asthma and grass pollen allergy who were under treatment with an ICS, 1 year of SCIT for grass pollen resulted in a slight but significant increase in the dose of grass pollen required to induce an EAR.³⁰ In another study, the improvement in NSBHR was more important in the

TABLE I. Published studies on the effects of AIT on nonspecific and specific BHR

Reference	Median patient age	Patients' phenotype	Type of AIT	Duration (mean ± SD)	Effect on nonspecific BHR	Effect on specific BHR	
						EAR	LAR
HDM							
Van Bever et al, 1988 ⁷	HDM AIT group 11.8 y (n = 19) GP AIT group 13.2 y (n = 12)	HDM- or GP-induced mild-to-severe asthma (a few patients under treatment with an ICS): HDM group Severe (n = 5) Moderate (n = 7) Mild (n = 7) GP group Severe (n = 5) Moderate (n = 3) Mild (n = 4)	HDM or GP SCIT	HDM: 47 ± 13 mo GP: 40 ± 11 mo	NA	↓Severity† HDM Overall: more severe drop in FEV ₁ in children with no HDM AIT; 11 of 32 (34%) had an FEV ₁ value of <50% GP No effect	↓Frequency ↓Severity† HDM Overall: LAR in 29% of children with AIT vs in 73% of children without AIT GP No effect
Van Bever et al, 1989 ⁸	10.9 y (n = 15)	HDM-induced mild-to-severe controlled asthma under treatment with an ICS and/or DSCG or theophylline	HDM SCIT	12 mo	NA	No change in PD ₂₀	↓Severity† ↓Frequency
Van Bever et al, 1992 ⁹	9 y (n = 18)	HDM-induced asthma Severe (n = 5) Moderate (n = 2) Mild (n = 2)	HDM SCIT	12 mo	No change in histamine PD ₂₀	↓Severity† Overall Small but significant change in median HDM PD ₂₀ (<1 doubling dose)	↓Severity† ↓Frequency
Ibero et al, 2006 ¹⁰	8-16 y* (n = 30)	HDM-induced mild asthma ± rhinitis, (monosensitization)	HDM SCIT	4 mo	NA	↓Frequency (12.8-fold) Increase in HDM Pc ₂₀	↓Frequency (dual responders)
Yukselen et al, 2011 ¹¹	10 y (n = 30)	HDM-induced persistent mild asthma (GINA) with allergic rhinitis	HDM SCIT (n = 10); SLIT (n = 10)	12 mo	NA	Significant increase in HDM PD ₂₀ in SCIT group	NA
Pifferi et al, 2002 ¹²	6-14 y* (n = 15)	HDM-induced mild-to- moderate asthma ± rhinitis (monosensitization)	HDM SCIT	36 mo	Change in methacholine PD ₂₀ (1 doubling dose)	NA	NA
Pischler et al, 1997 ¹³	28 y (n = 30)	HDM-induced asthma ± AR with a positive CPT result	HDM SCIT	12 mo	Change in PD ₂₀ (1 doubling dose)	NA	NA
Chang et al, 2001 ¹⁴	AR: 32 y (n = 16) BA: 37 y (n = 24) BA + AR: 33.4 y (n = 13)	Asthma ± AR under treatment with a β2-agonist only	HDM SCIT (n = 31) HDM SCIT + pollen (n = 22)	12 mo	Increase in methacholine PC ₂₀ (3 doubling concentrations) in groups with AR and AR + BA ↓frequency: 75% of AR, 41% of BA, 53.8% of AR + BA	NA	NA
Basomba et al, 2002 ¹⁵	21 y (n = 55)	HDM-induced mild-to- moderate asthma	HDM SCIT	12 mo	NA	Increase in HDM PD ₂₀ (2 doubling doses)	NA
Ameal et al, 2005 ¹⁶	23 y (n = 55)	HDM-induced mild-to- moderate asthma and rhinoconjunctivitis	HDM SCIT	12 mo	NA	Significant increase in PD ₂₀ (>2 doubling doses)	NA

(Continued)

TABLE I. (Continued)

Reference	Median patient age	Patients' phenotype	Type of AIT	Duration (mean ± SD)	Effect on nonspecific BHR	Effect on specific BHR	
						EAR	LAR
Garcia-Robaina et al, 2006 ¹⁷	24 y (n = 54)	HDM-induced mild-to-moderate asthma (GINA) with rhinoconjunctivitis	HDM SCIT	54 mo	NA	Increase in HDM PD ₂₀ (>2 doubling doses)	NA
Blumberga et al, 2011 ¹⁸	29 y (n = 54)	Moderate-to-severe asthma	HDM SCIT	36 mo	Increase in methacholine PD ₂₀ (1 doubling dose)	Increase in HDM PD ₂₀ (3 doubling doses)	↓ Frequency
Other allergens							
Taylor et al, 1977 ¹⁹	28 y (n = 10)	Cat-induced asthma	Cat SCIT	4 mo	No change in histamine PD ₂₀	No change in cat PD ₂₀	NA
Ohman et al, 1984 ²⁰	26 y (n = 9)	Cat-induced asthma	Cat SCIT	4 mo	No change in methacholine PD ₂₀	Increase in cat PD ₂₀ (>2 doubling doses)	NA
Sundin et al, 1986 ²¹	Adults (n = 21) and children (n = 20) with cat or dog asthma; 22 y	Cat- or dog-induced mild-to-moderate asthma ± rhinitis	Cat or dog SCIT	12 mo	Change in histamine PC ₂₀ (1 doubling dose) in cat AIT	↓ Frequency 11-fold increase in cat PC ₂₀	NA
Van Metre et al, 1988 ²²	21-52 y* (n = 22)	Cat-induced asthma	Cat SCIT	12 mo	No change in methacholine PC ₂₀	Increase in cat PD ₂₀ (>1 doubling dose)	NA
Haugaard et al, 1992 ²³	28 y (n = 24)	Cat- or dog-induced asthma	Cat SCIT (n = 12) Dog SCIT (n = 2) Cat and dog SCIT (n = 10)	12 mo	Increase in histamine PC ₂₀	Increase in cat PD ₂₀ (>1 doubling dose)	NA
Alvarez-Cuesta et al, 1994 ²⁴	24 y (n = 28)	Asthma and allergic rhinoconjunctivitis	Cat SCIT	12 mo	No change in methacholine PC ₂₀	↓ Frequency increase in cat PC ₂₀ (>1 doubling dose)	NA
Hedlin et al, 1995 ²⁵	Children (n = 20) and adults (n = 20)	Cat- or dog-induced asthma	Cat or dog SCIT	Long-term follow-up (5 y after 36 mo of AIT)	No change in histamine PC ₂₀	↓ Frequency 10-fold increase in cat PC ₂₀ No change in dog PC ₂₀	NA
Pène et al, 1998 ²⁶	28 y (n = 31)	Cat-induced asthma	Cat SCIT (<i>Felinus domesticus</i> 1)	6 wk	NA	No change in PD ₂₀	NA
Arvidsson et al, 2004 ²⁷	33 y (n = 19)	Mild asthma with rhinitis to birch pollen under treatment with a β ₂ -agonist only	Birch SCIT	12 mo	No change in methacholine PC ₂₀	Increase in PD ₂₀ No change in frequency	No change in severity
Dolz et al, 1996 ²⁸	18 y (n = 28)	GP-induced asthma ± allergic rhinoconjunctivitis	GP SCIT	36 mo	NA	Increase in GP PD ₂₀ (2 doubling doses)	NA
Möller et al, 2001 ²⁹	10.7 y (n = 42)	GP- and birch pollen-induced mild asthma with allergic rhinoconjunctivitis	GP and/or birch SCIT	36 mo	Significant change in methacholine PC ₂₀ during and out of pollen season	NA	NA
Roberts et al, 2005 ³⁰	9.2 y (n = 35)	GP-induced mild and moderate-to-severe asthma ± rhinoconjunctivitis	GP SCIT	24 mo	NA	Increase in GP allergen PD ₂₀	NA
Pajno et al, 2004 ³¹	11 y (n = 30)	<i>Parietaria</i> pollen-induced asthma	<i>Parietaria</i> SLIT	18 mo	Significant change in methacholine PC ₂₀ (1 doubling dose during pollen season)	NA	NA

(Continued)

TABLE I. (Continued)

Reference	Median patient age	Patients' phenotype	Type of AIT	Duration (mean $\pm$ SD)	Effect on nonspecific BHR	Effect on specific BHR	
						EAR	LAR
Dreborg et al, 1986 ³²	11 y (n = 30)	<i>Cladosporium</i> sensitization with allergic rhinoconjunctivitis and worsening asthma in June-October	<i>Cladosporium</i> SCIT	10 mo	NA	10-fold increase of <i>Cladosporium</i> concentration	NA

BA, Bronchial asthma; CPT, conjunctival provocation test; DSCG, disodium cromoglycate; GP, grass pollen; HCT, histamine challenge test; MCT, methacholine challenge test; NA, not applicable; NPT, nasal provocation test; PC₂₀, provocative concentration causing a 20% drop in FEV₁ from baseline.

*Age range (rather than mean age) is provided.

†Severity defined as change in the mean drop in FEV₁.

group of patients with asthma associated with rhinitis than in the group with asthma.¹⁴

To summarize, SCIT appears to have a clinical and significant effect on the EAR to mite, cat, and birch and grass pollens in children and adults. However, more data are needed, particularly regarding cat and pollen. DRs are poorly studied. In a few studies, particularly in children, a reduction in response to mite (and more surprisingly, to birch and grass) was obtained. These results were obtained in patients who had associated rhinitis and were under treatment with an ICS. The magnitude of the effect was close to those of other antiasthmatic drugs (eg, ICSs [with approximately 1 doubling of the dose of allergen]).

EFFICACY OF SLIT IN ADULTS WITH ALLERGIC ASTHMA: FIELD STUDIES

Study of the efficacy of sublingual immunotherapy (SLIT) in allergic asthma has demonstrated a long succession of improvements. Before 1990, most published studies included a small number of patients, and some of these studies had major methodologic limitations.² The first published meta-analysis of SCIT included 20 studies. The conclusion favored SCIT over placebo in symptom reduction and drug intake, and these results were later updated.³⁹⁻⁴¹ In the meantime, SLIT was introduced⁴² and the studies were relatively limited until the publication of large controlled studies on grass pollen^{26,43} and a meta-analysis demonstrating a positive effect of SLIT, particularly in pollen AR and conjunctivitis.⁴¹ However, the results obtained with mite allergen in adults with asthma were less convincing, likely owing to the nature of the studies and especially the small sample sizes.^{41,44} A major breakthrough was obtained with the publication of MT02, the *post hoc* analysis of the MT02 (efficacy and safety of a standardized quality allergen standardization HDM SLIT-tablet in adults and adolescents with HDM respiratory allergic disease) and MT04 (efficacy of house dust mite allergy immunotherapy tablet in subjects with house dust mite induced asthma) studies⁴⁵⁻⁴⁷ in which 604 adult subjects with allergic asthma due to mite were enrolled. An 81- μ g per day reduction in ICS dose was obtained. It was the first time that a large study of SLIT in adults with mite asthma showed a corticosteroid-sparing effect.⁴⁵ Interestingly, 72% of the patients were polysensitized to other indoor allergens, and all had a mild-to-moderate mite AR. There was no difference in efficacy between mite-mono-sensitized patients and those with indoor or outdoor polysensitization. A *post hoc* analysis of a subset of the trial study patients (108 patients) corresponding to 18% of the full analysis set (FAS), with a mean ICS dose of 615 μ g per day versus 449 μ g per day in the FAS, was performed.⁴⁷ The subjects were partly controlled at randomization with an Asthma

Control Questionnaire score of 1.15 for the 6 SQ-HDM and 0.77 in the FAS. A mean reduction in ICS of 327 μ g per day was obtained, and 59% of the patients reduced their ICS treatment by 75% to 100%, with preservation of lung function. These results were confirmed by another large double-blind control study in adults with asthma and mite allergy.⁴⁸ According to these studies, desensitization in cases of asthma due to mite allergy might best be targeted to 30- to 40-year-old patients who are polysensitized and have partly controlled asthma with a normal FEV₁ value and concomitant rhinitis. The MT04 study confirmed this hypothesis in 834 patients. Two-thirds of the patients were polysensitized, and all of them had concomitant rhinitis. Their symptoms were not well controlled by ICSs or combination products, with the Asthma Control Questionnaire score varying from 1.22 to 1.24 depending on the group. According to the GINA asthma control level, in 72% of the patients asthma was partly controlled and in 28% it was not controlled. This was a 7- to 12-month study followed by a period of ICS reduction of 50% and 100%. The primary objective was to evaluate the time to first moderate or severe asthma exacerbation. In the 2 arms with the tablets (6 SQU or 12 SQU), the risk of a moderate or severe asthma exacerbation was significantly reduced, the time to first exacerbation with deterioration in asthma symptoms or nocturnal awakening and the time to first exacerbation with deterioration in lung function were both increased, and the use of short-acting β 2 agonists was reduced compared with in the placebo group. However, in the same study, no significant reduction in severe exacerbations was observed, possibly because the trial was not designed or powered to detect effects on severe asthma exacerbations. A more recent Japanese study of 826 adults that compared HDM SLIT tablet treatment with placebo failed to demonstrate an effect on exacerbations or on symptom scores, lung function, or quality of life.⁴⁹ The National Asthma Education and Prevention Program 2020 update concluded that 3 randomized controlled trials of SLIT versus placebo favored the SLIT intervention for exacerbation reduction, but it found no difference between SLIT and placebo in terms of systemic corticosteroid use.⁵⁰

To summarize, HDM SLIT tablets demonstrate efficacy in asthma exacerbations and other outcomes when used as add-on therapy in adult patients with asthma and concomitant rhinitis due to mite. In contrast, the use of SLIT with other allergens in adults, whether given in drops or tablets, is not supported by a strong level of evidence.

EFFICACY OF SLIT IN CHILDREN WITH ALLERGIC ASTHMA: FIELD STUDIES

For decades, practicing allergists have observed an apparent benefit of AIT in pediatric patients with asthma and have long

speculated on the potential of the modality for preventing childhood asthma. However, the efficacy and safety of AIT for treating childhood asthma have yet to be rigorously evaluated in large well-powered double-blind placebo-controlled (DBPC) trials. Enthusiasm for using SCIT in pediatric patients is tempered by the potential risks of postinjection anaphylaxis, and this treatment is rarely started in children younger than 5 years.^{51,52} To date, SLIT tablets, 2 grass products, and 1 ragweed product have been proved to be safe and effective for seasonal AR and have received regulatory approval in children aged 5 years or older.⁵³⁻⁵⁵ In a pooled safety analysis of 9 pediatric DBPC trials that included 895 children and adolescents who received timothy grass pollen SLIT, epinephrine was administered in 3 patients; 1 severe systemic allergic reaction (with hypotension) was reported. The safety profile was similar in subjects across geographic regions and with and without asthma.⁵⁶ Similarly, a recent multicenter DBPC phase 3 study evaluating ragweed SLIT tablets for children with seasonal AR (involving 1022 children) reported no differences in treatment-related adverse events between those subjects with and without asthma (68.4% and 62.6%, respectively).⁵⁵ In this study, 2 subjects experienced mild and moderate systemic reactions related to SLIT. To date, no deaths due to anaphylaxis have been attributed to aeroallergen SLIT in any age group.

To date, no large DBPC studies have investigated the efficacy of SLIT in treating childhood asthma. Nevertheless, recent phase 3 trials of pediatric SLIT trials for seasonal allergic rhinoconjunctivitis have included substantial percentages of subjects with mild asthma (26%-40%). In some studies, exploratory asthma outcomes have been assessed. In the North American DBPC study of a timothy grass SLIT tablet for seasonal allergic rhinoconjunctivitis, 26% of 345 subjects had concomitant histories of asthma. The actively treated patients exhibited a 21% reduction in mean asthma daily symptom scores (DSSs) versus placebo, although these differences were not significant.⁵³ A phase 3 multicenter ragweed SLIT tablet study demonstrating efficacy and safety of ragweed seasonal allergic rhinoconjunctivitis in children (aged 5-17 years) assessed exploratory asthma outcomes such as DSSs in all subjects.⁵⁵ Subjects with a concomitant medical history of asthma (40% of the subjects) were evaluated for requirements for rescue albuterol and nighttime awakenings due to asthma. A relative improvement of 31% in mean DSS was observed with active treatment versus with placebo during the peak pollen season. Requirements for short-acting β -agonist use and nocturnal awakenings were significantly improved (by 68% and 75%, respectively) with active ragweed SLIT versus with placebo. Although this study was not designed or powered to investigate asthma, these results, combined with safety data in AR trials, lend support to conducting SLIT trials evaluating asthma outcomes as primary end points in pediatric populations.⁵⁶

Secondary prevention of childhood asthma by early initiation of AIT was supported by results of the Prevention of Asthma study.⁵⁷ This was the first controlled longitudinal study of children aged 6 to 14 years with grass pollen- and/or tree pollen-induced seasonal allergic rhinoconjunctivitis; the children were followed for 7 years after receiving 3 years of maintenance SCIT or no treatment intervention. The actively treated patients were significantly less likely to develop asthma when evaluated 7 years after treatment (odds ratio = 2.5 [95% CI 1.1-5.9]). The weaknesses of this study were lack of a true placebo arm, high number of dropouts over time, and reliance on a subjective asthma

outcome based on reported symptoms. Subsequently, a large 5-year DBPC study (ie, the GAP study) was conducted in 812 children (aged 5-12 years) with grass pollen-induced rhinoconjunctivitis; in the study, patients were randomized to 3 years of treatment with timothy grass pollen SLIT tablets or placebo and observed for 2 years after discontinuation of treatment.⁵⁸ No difference in the primary outcome, namely, time to onset of asthma defined by reversible airway obstruction, was observed. Significant reductions in asthma symptoms and medication requirements were observed in the SLIT-treated children compared with in the children who received placebo; the reductions occurred during both the active treatment and the 2-year follow-up phases of the study.

To summarize, use of AIT in children with asthma is widely practiced but not supported by as strong a level of evidence as in adults. SLIT has a better safety profile than SCIT and could be a promising therapy for mild or moderate asthma in children sensitized to seasonal and perennial aeroallergens. The role of AIT in prevention of asthma is unclear.

ROLE OF BIOLOGICS AS AN ADJUVANT TO ALLERGEN THERAPY

There are 3 major reasons to consider the use of a biologic in conjunction with AIT: to improve the safety of AIT; to provide better asthma control, allowing for the use of AIT; and to improve the efficacy of immunotherapy.

Currently, AIT is not recommended for patients with uncontrolled and/or severe asthma.⁵⁹ The risk of an anaphylactic event due to AIT in a patient with uncontrolled asthma is substantially higher.⁵⁹ Of the 5 currently US Food and Drug Administration-approved biologics, only omalizumab has been studied as an adjunctive therapy to improve the safety of AIT. Massanari et al evaluated omalizumab's effect on the tolerability of AIT in patients with symptomatic persistent asthma that was not adequately controlled with an ICS.⁶⁰ Patients were randomized to omalizumab or placebo (for 16 weeks), cluster AIT (a 4-week, 18-injection regimen to at least 1 of 3 perennial aeroallergens, including 3 weeks of overlap with omalizumab or placebo), and maintenance immunotherapy (for 7 weeks). The primary efficacy variable was systemic allergic reactions attributable to immunotherapy. Omalizumab was associated with fewer systemic allergic reactions to AIT and enabled more patients to achieve the target immunotherapy maintenance dose. Kopp et al studied the effect of omalizumab in combination with AIT in patients with seasonal allergic rhinoconjunctivitis and comorbid seasonal allergic asthma that were incompletely controlled by conventional pharmacotherapy.⁶¹ Omalizumab or placebo was started 2 weeks before the 18-week treatment with grass immunotherapy. Compared with AIT alone, the combination of omalizumab with AIT was safe and reduced the rhinitis and asthma symptom loads in a statistically significant and clinically meaningful manner. Neither study compared the therapeutic effects of the combination of omalizumab and AIT with those of a stepped-up asthma regimen with or without a biologic. Nonetheless, these limited data suggest that omalizumab pretreatment before AIT provides added safety and that the combination of omalizumab plus AIT provides better efficacy. On the basis of studies examining the onset of action of omalizumab to both block nasal allergen challenge responses and decrease IgE and the high-affinity IgE receptor on critical effector cells, the optimal duration

of omalizumab pretreatment to impart added safety to AIT appears to be about 8 weeks.^{62,63} There are no data on using other biologics to improve the safety and efficacy of environmental AIT. From the standpoint of mechanism of action, an anti-IgE or mast cell inhibition therapeutic approach makes the most sense for use as a pretreatment to enhance the safety of AIT.

Using a biologic to improve the patient's lung functions and asthma control before initiating AIT can turn unsuitable candidates for AIT into appropriate candidates; however, there are no randomized DBPC studies examining this hypothesis from the standpoint of the ability of biologics to improve lung function, asthma control, and exacerbation rates.⁶⁴ This approach appears logical to implement in clinical practice. Furthermore, because all 5 approved biologics can improve asthma control, the recommendation to use a given biologic over another is not supported by data. There are limited data on stopping omalizumab or any other biologic once a patient is receiving maintenance AIT. Clearly, there might be an added risk involved in such an approach.

HIGH T2 AIRWAY INFLAMMATION AND CORRELATION WITH A DR FOLLOWING ALLERGEN CHALLENGE

The development of personalized medicine raises the question of whether the individual phenotypes of some patients with asthma make them more or less likely to respond to AIT. Considering that BCT is a useful tool for evaluating antiasthmatic drugs, patients with allergy who develop a DR appear to be more likely to respond positively to AIT. Indeed, the immune and inflammatory processes of the LAR involve an increase in type 2 (T2) airway inflammation induced by allergen exposure, in which case eosinophils appear to be predominant through their ability to release proinflammatory lipid mediators and cytokines. Airway eosinophilia has been associated with poor asthma control,⁶⁵ and blood eosinophils have been associated with lung function decline.⁶⁶ Several studies have shown that the LAR is associated with a pronounced airway eosinophilia when compared with the EAR only after an allergen challenge test,⁶⁷⁻⁷¹ with a correlation between the size of the LAR and the degree of airway eosinophilia.^{72,73} After allergen exposures, significant differences were also observed in terms of systemic inflammation, particularly in individuals with dual asthmatic-responses, who had increased blood eosinophilia compared with EAR-only individuals⁷³⁻⁷⁶; in addition, differences are observed in circulating eosinophil progenitors at 12 and 24 hours.⁷⁶⁻⁷⁹ Furthermore, allergen inhalation causes upregulation of the IL-5 receptor on bone marrow eosinophil progenitors and bone marrow IL-5 protein levels.^{76,78} This is in accord with the natural exposure to allergen. Eosinophil activity increases with exposure to birch allergen,⁸⁰ as well as during repeated low-dose exposure to cat allergen, mimicking natural exposure, which induces increases in eosinophil cationic protein (ECP) levels in serum and bronchoalveolar lavage fluid.⁸¹ However, although the mean serum ECP level has been reported to increase during the birch pollen season in patients with birch allergy, this has not been true for all patients.⁸⁰ In addition to the increase in eosinophil numbers, an increase in neutrophil and basophil numbers was also observed.⁸²⁻⁸⁴

The T2 response is also characterized by T lymphocytes of the T_H2 cell phenotype, which are central orchestrators of airway inflammation in asthma.⁸⁵ They are recruited to the bronchial

mucosa through the expression of C-C chemokine receptor type 4 (CCR4) and its ligands (thymus and activation-regulated chemokine [TARC] and macrophage-derived cytokine [MDC])^{86,87} and specific cell adhesion molecules.⁸⁸ Lymphocytes have been associated with the LAR, and activated T cells together with their cytokines play critical roles in the local accumulation and activation of eosinophils. In HDM allergic asthma, dual responders show a trend toward higher lymphocyte numbers ($P = .053$) in their sputum than in the sputum of early responders.⁸⁹ An increase in IL-2R, a marker of lymphocyte activation, has been correlated with the decrease in FEV₁ during the LAR ($r = 0.48$; $P = .050$), suggesting that lymphocytes are activated by allergen challenge and are also closely involved in pathogenesis of the LAR.⁹⁰ *In vitro*, the allergen-specific proliferative response of peripheral T lymphocytes was correlated significantly ($r = 0.44$; $P = .04$) with the magnitude of the LAR and with serum IL-5 level after BAC ($r^2 = 0.48$; $P = .02$).⁹¹ Dual responders had greater production of T_H2 chemokines, such as TARC, MDC, IL-5, and IL-13 (in bronchoalveolar lavage fluid) after allergen challenge, suggesting that T_H2-type chemokines may contribute to the persistence of eosinophilic airway inflammation through lymphocyte recruitment.⁹² IL-9, a T_H2 cytokine produced mainly by lymphocytes, is upregulated after local allergen challenge in the lungs and is correlated with eosinophil numbers, suggesting a potential role for IL-9 in the LAR,⁹³ although its function in human asthma is poorly understood.⁸⁵

Other lymphocytes, such as group 2 innate lymphoid cells (ILC2s), have been shown to increase after allergen challenge. An increase in total, IL-5-positive, IL-13-positive, and prostaglandin D₂ receptor 2 (CRTH2)-positive ILC2 numbers was found in sputum, 24 hours after allergen exposure and was correlated with allergen-induced changes in IL-5-positive CD4⁺ cells,⁹⁴ suggesting a role for them in the DR. However, to our knowledge, there have been no studies of these cells that have distinguished between the types of asthmatic response (DR or isolated EAR).

With regard to negative regulation, studies have suggested that regulatory T cells, a suppressive lymphocyte population, are deficient in subjects exhibiting a DR, resulting in an impaired ratio of T_H2 effector and regulatory cells,^{95,96} and that compared with controls, patients with eosinophilic asthma are deficient in regulatory T cells.⁹⁷

In summary, dual responders appear to respond to allergen exposure with a high T2 response driven by inflammatory eosinophils and T_H2 lymphocytes.

THE ROLE OF RHINITIS

In most clinical studies, AIT has been effective in patients with asthma and concomitant rhinitis. AR is strongly linked to asthma and often precedes its onset. Subjects with rhinitis have a risk of asthma that is approximately 32 times higher than that of the control population, and about 75% of asthma cases are associated with rhinitis.⁹⁸ However, some patients have AR alone, other patients have AR and asthma, and a few patients have asthma alone; the phenotype of AR that can lead to asthma is still unclear.⁹⁸ The concept of a "united airway" was introduced more than 2 decades ago.⁹⁹ In this concept, a systemic inflammatory response plays an important role in the AR-asthma relationship.¹⁰⁰ Several studies have shown that a nasal allergen challenge is able to elicit systemic and pulmonary T2 inflammation characterized by eosinophils; increased NSBHR; and activation of circulating

basophils, lymphocytes, and plasmacytoid dendritic cells. The inverse link (asthma to nose) has been suggested but is less well demonstrated.¹⁰¹ There are probably common genes associated with asthma and AR, as well as specific genes associated with AR alone. A recent hypothesis emphasizes the epithelium-derived cytokines/alarmins IL-25, IL-33, and TSLP as key regulatory factors linking innate and adaptive immunity and the immune pathogenic mechanisms of AR, chronic rhinosinusitis, and asthma, mainly involving T2 inflammatory responses.¹⁰² These mediators have been associated with the polysensitization and multimorbidity that represent the extreme allergic phenotype, starting early in life, pointing to T2 inflammation¹⁰³ and eosinophil activation.¹⁰⁴ European network for the PHenotyping of Occupational Asthma (E-PHOCAS), it was found that in occupational asthma due to high-molecular-weight allergens, a relationship exists between rhinitis and higher sputum eosinophil numbers after BCT (manuscript in preparation). Taking into account the indirect arguments in favor of a relationship between AR and T2 inflammation, one can speculate that these patients would more frequently be dual responders.

WHAT IS THE BEST MARKER TO DEFINE SUCH PATIENTS?

It seems difficult to use the blood or sputum eosinophil count as a marker of an elevated T2 response, because not all subjects with allergic asthma have eosinophilic asthma at baseline. As shown by Revez et al,¹⁰⁵ in allergic asthma 38% of cases are paucigranulocytic, 43% are eosinophilic, 9% are neutrophilic, and 9% are mixed granulocytic in induced sputum. The type of allergen sensitization is not a significant factor associated with the eosinophilic phenotype.¹⁰⁶ However, the sputum inflammatory subtype can change, and subjects with baseline paucigranulocytic sputum developed eosinophilic (48%) or mixed granulocytic (43%) sputum after allergen challenge.¹⁰⁵ Similar results were found in occupational asthma. A majority of patients with occupational asthma with a positive specific inhalation challenge result had increased numbers of eosinophils in induced sputum after the exposure.¹⁰⁷

HOW DOES AIT AFFECT EOSINOPHILS?

If we consider that T2-high responders to allergen exposure to be good candidates for AIT in asthma, does desensitization have an effect on eosinophils? Some studies have demonstrated such an effect of AIT. In subjects with HDM asthma, SCIT induced significantly lower levels of sputum eosinophils (before and after a nasal provocation test) versus in patients who were not receiving AIT ($P < .05$).^{11,108} *In vitro*, AIT induces the suppression of antigen-dependent production of eosinophil chemotactic activity from PBMCs and attenuates eosinophil transendothelial migration induced by antigen-stimulated mononuclear cells.^{109,110} In asthma due to birch allergy, AIT protects from the increase in eosinophils and ECP after allergen challenge²¹ and in ECP during the pollen season.¹¹¹ In grass pollen immunotherapy, symptomatic improvement was correlated with reductions in eosinophil numbers and IL-5 mRNA expression in the nasal mucosa during the pollen season.¹¹² In grass pollen allergic asthma, Jakwerth et al¹¹³ demonstrated that AIT induces a significant reduction in sputum eosinophil and ILC2 numbers compared with the numbers in untreated patients, as well as in the expression of

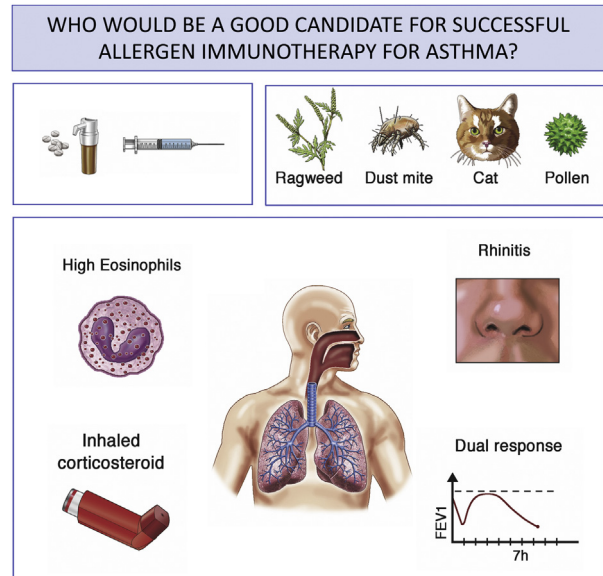


FIG 1. Who would be a good candidate for successful AIT for asthma? Graphical representation of the good candidate for AIT: a patient with allergic asthma who is treated for AR with corticosteroids and who develops a DR with high eosinophilic inflammation after allergen exposure.

the prostaglandin EP3 receptor and its ligand prostaglandin E₂ (PGE₂). PGE₂ levels were correlated with ILC2, sputum IL-13, and eosinophil numbers, as well as with symptom burden, suggesting that the PGE₂ receptor EP3 is involved in AIT-mediated mechanisms in asthma.

CONCLUSION

Much progress in AIT has been achieved since the first publication on SLIT in 1994. Most of the effort has been concentrated on AR, and large controlled studies have been published. For allergic asthma, however, only 1 large study on mite allergy has clearly shown the efficacy of AIT. It is time to accelerate research on this topic. Because allergy is a personalized medicine, increasing the benefit of treatment necessitates phenotyping the most appropriate patient. According to the results of field studies in adults and children, polysensitized patients who have concomitant rhinitis of GINA class 2 to 4 severity and who need ICSs appear to have the best chance of being good responders. However, among this group, a subgroup would be likely to improve while undergoing AIT (Fig 1); that is, those individuals who demonstrate a high response of activated eosinophils to natural or experimental exposure would be those in whom allergen exposure induces the most important T2 response. Performing experimental allergen exposure before initiating an AIT would be difficult for practical reasons. However, measuring an increase in the numbers of activated eosinophils in the blood before and during natural exposure appears more realizable for seasonal allergens. For perennial allergens, it would be interesting to validate blood markers of T2 inflammation that are correlated with activation of the eosinophils using experimental allergen exposure. Because induced sputum is time consuming and difficult to perform routinely, measurement of serum ECP before and after a specific inhalation test can be challenging.

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