

22 Subcutaneous Immunotherapy for Allergic Rhinoconjunctivitis, Allergic Asthma, and Prevention of Allergic Diseases

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INTRODUCTION

Allergic rhinitis, the most common allergic disease, affects about 20% of the adult population (1). Allergic asthma varies in prevalence in different countries, but in the Western world it usually affects more than 5% of the population (2). These diseases, which predominantly affect children and young adults, impair both physical and cognitive functions and quality of life (3). The anatomy and physiology of nasal and bronchial mucosa are very similar, and most patients with allergic asthma also have rhinitis (4). The coincident upper and lower airway dysfunction suggests a continuum of disease between rhinitis and asthma. This is the basis for the concept that the upper and the lower airways be considered a single entity, influenced by a common and evolving inflammatory process, which may be sustained and amplified by interrelated mechanisms (5).

Allergic rhinitis constitutes a major risk factor for development of allergic asthma with approximately 20% of patients with allergic rhinitis subsequently developing asthma (3,6,7). Patients with upper airway disease and associated bronchial hyperreactivity (BHR) are more likely to develop asthma (8,9).

OBJECTIVES OF ALLERGEN-SPECIFIC IMMUNOTHERAPY IN ALLERGIC DISEASES

Allergic rhinitis, especially in seasonal pollen allergy, is a disease in which allergy is the dominant or single eliciting factor, and consequently allergen immunotherapy is more likely to be highly effective. Asthma is a multifactorial and more complex disease in which allergic factors and nonallergic triggers interact and result in bronchial obstruction and inflammation (10). The inhalation of allergens leads to a complex activation of various cell types and the release of proinflammatory mediators. On the basis of allergen sensitization, different situations exist in indoor (house dust mites and animal dander) and outdoor allergy (mostly pollens). Although very few pollen grains can reach the lower airways, these allergens, carried on fragmented pollen or other particles (usually less than 10 μm in diameter), frequently induce asthma via an IgE-mediated mechanism (10,11). Pollen-induced allergic reactions, prolonged over several days, almost always lead to nonspecific BHR. This BHR is usually transient in patients allergic only to pollens, lasting from a few weeks to a few months after the end of the pollen season (12). House dust mites and other indoor allergens induce a sustained inflammation of the bronchi leading to variable BHR. Symptoms are caused by a combination of allergen-induced inflammation and specific and nonspecific BHR (13). The persistent allergen exposure results in a chronic, persistent inflammatory state. Some patients with chronic asthma develop airway remodeling or irreversible structural changes (14). Inflammation and airway remodeling may be involved in the "accelerated decline" of the pulmonary function characterized by a poorly reversible bronchial obstruction appearing after decades of chronic asthma (15). Loss of lung function is associated with permanent bronchial wall

alterations revealed by CT scans (16). The role of allergy in airway remodeling is not definitely defined.

These points suggest that (i) allergen-specific immunotherapy may be more rapidly effective in patients allergic to pollens than in those sensitized to indoor allergens; (ii) after a long course of the disease, patients with persistent asthma may have permanent airway abnormalities that cannot be reversed by allergen immunotherapy; (iii) grass pollen or other predominately seasonal pollen allergy may be an ideal model to study the effects of immunotherapy in patients with normal bronchi; and (iv) immunotherapy in mite allergy may be used to examine the effects of treatment in patients with a variable degree of bronchial inflammation and remodeling (17).

The major objectives of the immunomodulation of allergen immunotherapy are to reduce the allergic triggers eliciting symptoms in the short term and to decrease airway inflammation and BHR in the long run. This treatment ideally is prior to significant bronchial damage. Allergen immunotherapy appears to be the only treatment that modifies the course of the disease, either by preventing the development of new sensitivities or by altering the natural history of allergic airway diseases.

TREATMENT STRATEGY

The management of allergic airway diseases is based on combining three essential interventions, allergen avoidance, pharmacological treatment, and allergen-specific immunotherapy, with education of the patient on the nature of the disease. Education should include identification of triggers and relievers, appropriate variation of drug treatment, and recognition of disease involvement of the lower airways when appropriate (3). Nonspecific interventions are not restricted to the causative allergen but rather to the avoidance of nonspecific triggers. Specific interventions include avoidance of the causative allergen and application of allergen-specific immunotherapy.

The relative advantage of each of these three interventions, allergen avoidance, pharmacotherapy, and allergen immunotherapy, is variable, but the combination of interventions should improve the clinical outcome. Allergen avoidance always is the first-line attempt and may reduce the need for additional intervention even when not completely effective (18). A meta-analysis does not confirm the efficacy of single measures (19). A multifaceted intervention in selected subjects may be effective, but more data are needed. Drug treatment is often the next step to reduce symptom severity. However, for patients with a constant need for preventive (local steroids) pharmacotherapy, early initiation of allergen immunotherapy is advantageous, while the severity of the disease is modest and when the possibility for prevention of asthma is greatest (20,21). Allergen immunotherapy interferes with the pathophysiological mechanisms of allergic inflammation, with a potential for a prolonged effect compared with symptomatic pharmacological treatment (20,21). Although drugs are highly effective and with limited side effects, they represent a symptomatic treatment, while immunotherapy represents the only treatment that might alter the natural course of the disease (22). Using an appropriate allergen vaccine for correct indications, immunotherapy will significantly reduce the severity of the allergic disease, reduce the need for antiallergic drugs, and consequently improve the quality of life for allergic patients (23,24).

A significant proportion of subjects with persistent rhinitis have inflammation in the lower airways during allergen exposure (25). The symptoms from the lower airways often do not disturb the patients and the inflammation is therefore inconsistently or insufficiently treated. Allergen immunotherapy, as a solitary treatment, may ameliorate inflammatory reactions independent of the shock organ, that is, the treatment potentially will help rhinitis and simultaneously improve asthma or BHR. Consequently, considering the allergen-IgE-mediated disease as a multiorgan disease, it is important to consider immunotherapy based on the allergen sensitization rather than the disease or symptoms (21). The advantage of combining allergen avoidance, immunotherapy, and drug treatment requires further investigation, focusing on patient compliance, long-term preventative aspects, and cost-effectiveness/side effects.

The advantages of introducing allergen-specific, disease-modifying interventions (allergen avoidance and immunotherapy) in allergic disease management should be considered

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when developing a treatment strategy. It is advantageous to apply a specific treatment to interfere with the activation of the immunological mechanisms rather than to only treat symptoms. Furthermore, the exclusive use of drug treatment may affect the identification of specific allergen sensitization in the future by partially masking the association of allergen exposure and symptoms. Allergen identification is essential for prescribing specific treatment. Moreover, the lack of knowledge concerning the specific allergens reduces the possibility of avoiding allergens.

New insights into allergic inflammation provide a platform for further investigations of the advantages and drawbacks of different intervention strategies and for the development of new, effective and safe treatment principles. Conventional immunotherapy using native allergen extracts may in the future be substituted by a more refined and precisely targeted, allergen-specific immunological intervention based on knowledge of immunological mechanisms. One example of this approach is the use of recombinant allergens for immunotherapy.

ESTIMATING CLINICAL EFFICACY OF SUBCUTANEOUS IMMUNOTHERAPY

Allergic patients suffer from the clinical manifestations of the disease, i.e., rhinitis, conjunctivitis, and asthma, and clinical efficacy should reflect a significant reduction in disease severity (26). Consequently, only randomized, placebo-controlled clinical trials can be used to evaluate efficacy. The primary end point, if possible, should be a single end point, globally assessing the patient and the comorbidities. In the case of allergic rhinitis induced by pollens, the total symptom score including all nasal symptoms (nasal obstruction, rhinorrhea, sneezing, and pruritus) with one or more ocular symptoms is preferable. The use of rescue medication reflects symptom severity. Therefore, a primary end point may include both symptom severity and intake of rescue medications. Different approaches to combine the two scoring systems have been proposed, but there is no standardized method. For pollen allergy, the pollen count is important and the clinical efficacy of allergen immunotherapy should preferably be recorded during the entire pollen season. However, the primary outcome analysis can be made for the peak of the pollen season, represented for instance by the weeks including 50% of the total pollen load. House dust mites and animal dander can induce both intermittent and persistent symptoms, thus, the patients with persistent rhinitis and/or asthma should be carefully selected for study (27). For evaluating efficacy in asthma, bronchial symptoms (wheezing, shortness of breath, cough) can be used as a primary outcome, but a less subjective measure, such as FEV₁ or peak flow, is usually included as a co-primary end point. As secondary outcomes, the control of the disease and quality of life appear to be important parameters. Other outcomes, such as nonspecific BHR, may complement the study. Changes in immunological parameters and response to airway or mucosal challenge may be of interest in elucidating mechanisms but cannot replace the clinical evaluation.

The magnitude of clinically significant efficacy, clinically relevant reduction in disease severity, may be debated. By including a large number of participants, statistically significant but clinically irrelevant differences may be observed. The magnitude of efficacy should be relevant, i.e., the reduction in symptom scores and drug consumption should, from a clinical point and patient perspective, significantly reduce the morbidity of the disease. A review of 68 placebo-controlled, double-blind (PCDB) subcutaneous immunotherapy (SCIT) studies providing symptom/medication scores (26) suggests that a mean reduction in disease severity of >30% above the placebo effect is clinically relevant. Depending on the risks of intervention, costs, patient preferences, and inconvenience, this figure is subject to change.

When evaluating the clinical efficacy of interventions, the study design is critical to providing conclusive answers. The primary and, when appropriate, secondary outcome measures should be clearly defined. The sample size should be large enough to have a high probability (power) of statistically detecting a clinically important difference. Patients should be randomized to study groups to avoid bias in group characteristics, and the study should be a PCDB trial (27).

The majority of studies evaluating clinical efficacy focus on short-term efficacy, i.e., efficacy obtained during active treatment, often after a rather short period of treatment for one-half to one year. This degree of efficacy is important, but a major argument for instituting

allergen immunotherapy is to obtain long-term disease modifying capacity and to prevent disease progression.

CONTROLLED STUDIES TO DEMONSTRATE EFFICACY

Published studies indicate that SCIT is an effective treatment of allergic airway diseases, under the conditions of a careful selection of patients and the use of quality allergen extracts for treatment vaccines (26). In 1998, the author reviewed all double-blind, placebo-controlled immunotherapy studies of rhinitis or asthma. The evaluation criteria stipulated that the studies were peer reviewed, printed in English, included symptom-medication scores, and published since 1980 (26). The reason for not including older studies is that this arbitrary limit coincides with a general use of vaccines constituted from adequately standardized allergen extracts. Clinical efficacy was estimated by symptom-medication scores or by measuring the area under the curve of symptom-medication scores during the study period for both the active group and the placebo group (Fig. 1). The magnitude of improvement induced by active treatment was calculated as the percentage reduction in disease severity (symptom-medication scores) compared with placebo treatment. In 43 studies fulfilling the strict inclusion criteria, a mean clinical improvement of 45% greater than placebo was observed in 1120 actively treated subjects. Prior to the analysis, an improvement of at least 30% (mean) was arbitrarily chosen as the lower limit for clinical efficacy based on statistical significance and for balancing a clinically relevant efficacy with the inconvenience and risks of injection immunotherapy. Thus, the studies showed a clinically significant mean improvement.

An update of the original review (MedLine search terminated June, 2007) identified 59 double-blind, placebo-controlled studies, giving 65 comparable groups as some studies include more than one actively treated groups, evaluating the clinical efficacy of SCIT in rhinitis and 21 (25 comparable groups) in asthma (Malling H-J, personal communication). The update confirms the conclusion of the initial review (26) but adds birch and other pollens to the list of effective allergen vaccines. To evaluate efficacy an approach relying on statistical change was used. Studies are graded as "unequivocal efficacy" in the situation that both symptom scores and drug scores show a statistical significant difference between active treatment and placebo. In studies where either symptom scores or drug scores show a statistical significance, the grading "possible efficacy" is used (these studies probably are effective, but the documentation is not as convincing). Studies without statistical significance between treatment groups are graded as "no efficacy." For rhinitis, 8% (5 out of 65 comparable groups) were graded no efficacy, 6% (4 of 65) possible efficacy, and 86% (55 of 65) efficacy. For asthma the figures are no efficacy in 16% (4 of 25), possible efficacy in 20% (5 of 25), and efficacy in 64% (16 of 25). The mean clinical effect in these studies is a reduction in rhinitis severity of 40% and asthma severity of 45%, comparable with the 45% originally described. Including studies published since the original review (26), the additional number of actively treated patients

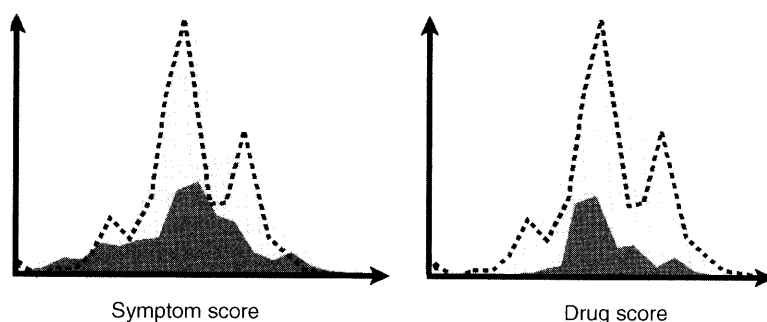


Figure 1 Magnitude of clinical efficacy estimated by measuring the area under the curve of immunotherapy treated (darkly shaded areas) as percentage of placebo treated (lightly shaded areas). The median symptom score and medication score of the immunotherapy group is 39% and 28% of the placebo group, respectively, indicating a mean reduction in symptoms of 61% and of 72% in medication scores. The dotted line denotes airborne grass pollen counts. Source: Data adapted from Ref. 52.

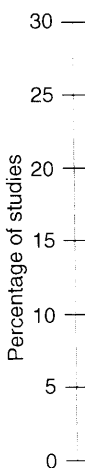


Figure 2 immunotherapy 477 asthma studies. Furthermore, difference in statistical significance between difference

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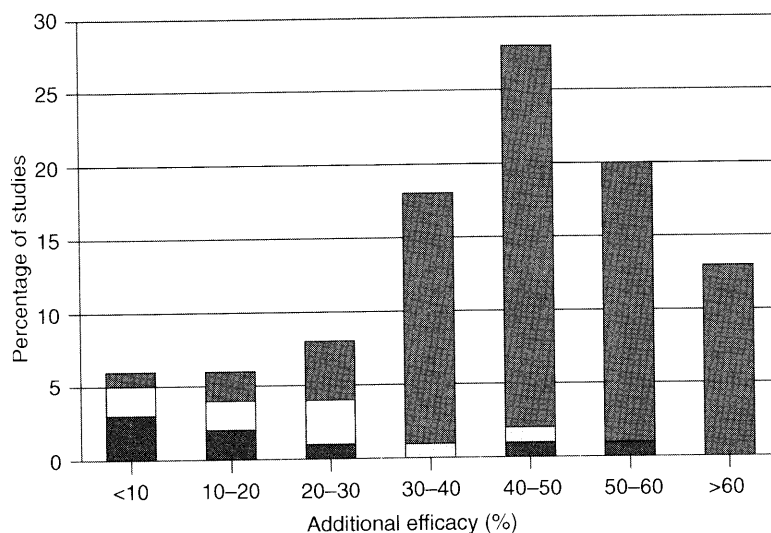


Figure 2 (See color insert.) Graded magnitude of clinical efficacy of placebo-controlled, double-blind rhinitis immunotherapy studies published in 1980–2007, including 2253 actively treated patients (1776 rhinitis patients and 477 asthma patients). The additional efficacy compared to placebo is given in intervals of 10%. The 80 clinical studies result in 90 groups comparable with placebo as some studies include two actively treated groups. Furthermore, the statistical significance is related to the magnitude of efficacy: green indicates significant difference from placebo for both symptom scores and drug scores (clear cut clinical efficacy), yellow indicates significance for either symptom scores or drug scores (possible clinical efficacy), and red indicates no significant difference for either symptom scores or drug scores (no efficacy).

brings the total number of patients supporting the evidence of efficacy to about 2250. Figure 2 shows the relation between the magnitude of efficacy (in 10% intervals) and the grading system based on the statistical analysis. If the original choice of 30% improvement more than placebo is chosen as a clinically significant threshold to justify the inconvenience of SCIT (26), then almost 80% of published studies in 2007 document a benefit with SCIT. This magnitude of efficacy is equivalent to or better than intranasal corticosteroids and considerably better than antihistamines or leukotriene inhibitors (3,28).

The allergens in the studies reviewed include seasonal pollens in 74%, dust mite in 19%, and animal danders and molds in less than 5% (Fig. 3). Pollen allergens, especially grass and ragweed, have the best documentation for efficacy. The efficacy for dust mite immunotherapy is convincing, but careful selection of candidates is crucial. The number of studies using animal danders and molds is insufficient for confident conclusions.

Pollen Allergens

The best documentation for efficacy of SCIT is in pollen allergy. The majority of patients suffer from rhinitis that may be complicated by asthma with high pollen exposure. Efficacy seems greater for asthma developing in subjects with allergic rhinitis than in subjects with asthma without rhinitis. This is probably due to the shorter duration of the allergic asthma symptoms and limited airway remodeling (29). Studies documenting clinical efficacy have been carried out with allergen vaccines of grass, ragweed, birch, mountain cedar, *Parietaria*, cypress, and other pollens. The dose dependency for clinical efficacy, based on natural exposure to grass pollens, is documented in one large-scale study (24).

An interesting non-placebo-controlled, but double-blind, comparative study evaluated the clinical efficacy of preseasonal birch pollen immunotherapy versus nasal glucocorticosteroid administered as budesonide, 400 µg daily (30). Symptom scores in the two groups were identical during the first four weeks of the six-week season, and only during the final two weeks did nasal glucocorticosteroid-treated subjects show fewer symptoms than immunotherapy-treated subjects. No difference in medication scores was observed indicating that a short course of preseasonal immunotherapy is almost as effective as this relatively high-dose

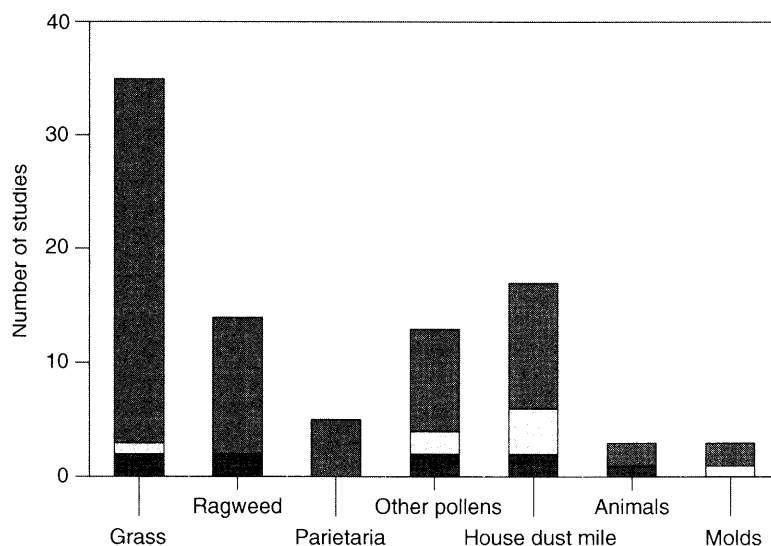


Figure 3 (See color insert.) Allergen vaccines used in placebo-controlled, double-blind rhinitis immunotherapy studies published in 1980–2007. Clinical efficacy is graded based on statistical significance (green indicated significance for both symptoms scores and drug scores (clear cut clinical efficacy), yellow indicates significance for either symptom scores or drug scores (possible clinical efficacy); and red indicates no significant difference for either symptom scores or drug scores (no efficacy).

intranasal glucocorticosteroid. An additional effect of immunotherapy, reinforcing that it represents a systemic treatment with effect on both the upper and the lower airways, was that seasonal peak expiratory flow values decreased significantly only in the nasal glucocorticosteroid-treated subjects. Furthermore, only immunotherapy prevented the seasonal BHR and eosinophil activation in asthmatic subjects.

House Dust Mite Allergens

Inhaled house dust mite allergen may induce both rhinitis and asthma in the same patient. Most studies evaluating the clinical effect of house dust mite immunotherapy use asthma as the indication. On the basis of clinical symptoms and medication scores, clinical efficacy is documented for house dust mite immunotherapy using vaccines from both *Dermatophagoides pteronyssinus* and *D. farinae*. House dust immunotherapy reduces bronchospasm following bronchial challenges with house dust mite extracts and increases the threshold dose to elicit immediate bronchial obstruction. Finally, the late-phase reaction following bronchial challenge with house dust mite is inhibited in many studies after SCIT (31). The decrease in the late-phase reaction is important as it indicates a decrease in the inflammatory reaction in the airway mucosa. However, some of the results with house dust SCIT are not impressive and, especially in adults, are sometimes negative. Subjects with house dust mite asthma often have perennial symptoms with occasional exacerbations, and the relative contribution of house dust mite sensitization to clinical symptoms may be difficult to determine. The variable role of allergen sensitization in determining symptoms with perennial allergic disease may be the reason for negative studies with SCIT. The glucocorticosteroid-sparing effect of SCIT was shown in a study demonstrating no improvement in asthma symptoms (32). Patients requiring at least the equivalent of 500- μ g inhaled fluticasone propionate daily were included; and in patients with moderate persistent asthma, the reduction in inhaled corticosteroids was statistically significant for those treated with SCIT compared with placebo after year 2 and year 3. The median dose reductions after three years were 90% for SCIT and 42% for placebo ($p = 0.04$).

The importance of the allergen dose required to induce a significant clinical effect has been investigated with house dust mite allergen (33). Using a maximal dose of 7 μ g of Der p 1, subjects experienced significant improvement in $PD_{20}FEV_1$ (provocative dose sufficient to decrease FEV_1 by 20%), but the maximal effect was observed with a dose of 21 μ g of Der p 1. Pretreatment asthma severity is critically related to the outcome of immunotherapy. Subjects

with severe asthma, FEV₁ under 70% of predicted values after optimal pharmacological treatment, demonstrated less improvement with immunotherapy than those with milder asthma (34).

Other Allergens

A number of studies demonstrate significant improvement in bronchial sensitivity, clinical symptoms, and medication needs in subjects with cat-allergic asthma following cat immunotherapy (35–37). Immunotherapy with dog is not validated, with no studies documenting clinical efficacy (38).

Immunotherapy studies with several allergens or potential allergens have not shown consistent benefit. These include most molds (39), *Candida albicans*, *Trichophyton*, and bacterial vaccines. This may be the result of poor quality of the extracts for many of these antigens. However, SCIT with standardized *Cladosporium* and *Alternaria* vaccines is highly effective in rhinitis and/or asthma in two studies (40,41), although less effective in a third (42). DBPC studies of SCIT with bacterial vaccines for treatment of rhinitis and/or asthma do not show efficacy (43). There is no study of immunotherapy with *C. albicans* or *Trichophyton*, and the quality of the extracts is generally inadequate.

Multiple Allergens

Few studies have investigated SCIT with multiple allergens. A controlled trial of SCIT, using a mixture of allergens, for treatment of mild to severe asthma in a population of optimally treated allergic children shows no significant difference compared with placebo (44). There are several methodological factors that may have led to the negative results. Among them, the study was carried out using mixtures of allergens including mold extracts, some potentially important allergens were not used, the dose of individual allergens was below the optimal dose, and the population of asthmatic children was not optimally selected (21). A major difference between American and European allergists/immunologists is the use of allergen mixtures in SCIT. Mixing of unrelated allergens is not recommended in Europe (45), whereas this is common practice in the United States (46). Mixing of allergens has not been documented to be effective in clinical studies, but existing data are insufficient to judge if mixed SCIT is effective (47,48). Other than mixing allergens in a vaccine that result in mutual degradation or diluting the dose of each allergen below the optimal dose, there is no rationale to explain why mixed vaccines would not be effective with SCIT.

Meta-Analysis

Using the Cochrane methodology, meta-analysis documents that SCIT for respiratory allergy is effective for both seasonal rhinitis (49) and asthma (47). The meta-analysis for rhinitis only includes pollen allergens. The rhinitis analysis identifies 51 studies fulfilling the inclusion criteria, but the data on symptom scores is based on only 15 trials. The overall reductions in symptom scores and medication scores are statistically significant, with a standard mean difference (SMD) of -0.73 (95% confidence interval, -0.97 to -0.50) for symptoms and -0.57 (95% confidence interval, -0.82 to -0.33) for medication scores in 13 trials.

Interpretation of the clinical importance of the effect size is difficult. The authors' interpretation is that "SCIT in suitable selected patients with seasonal allergic rhinitis results in a significant reduction in symptom scores and medication use. SCIT has a known and relatively low risk of severe adverse events."

The updated asthma analysis includes 75 randomized, controlled trials (47). There are 36 trials of SCIT with house dust mite, 20 with pollen extracts, 10 with animal dander, two with *Cladosporium*, one with latex, and six trials with a mixture of multiple allergens. Concealment of allocation was assessed as clearly adequate in only 15 of these trials. Significant heterogeneity among these 75 trials was evident in a number of comparisons. Overall, there was a significant improvement in asthma symptoms, SMD -0.72 (95% confidence interval, -0.99 to -0.33), and medication use, SMD -0.80 (95% confidence interval, -1.13 to -0.48). SCIT reduced allergen-specific BHR with some reduction in nonspecific BHR. There was no consistent effect on pulmonary function with SCIT. The reviewer's conclusions are that "immunotherapy reduces asthma symptoms and use of asthma medications and improves bronchial hyperreactivity. One trial found that the size of the benefit is possible comparable to inhaled steroids. The possibility of adverse effects (such as anaphylaxis) must be considered."

On the basis of meta-analysis, the documentation for efficacy of SCIT is evidence based with the strength of A for both rhinitis and asthma (50).

LONG-TERM EFFICACY AND ALTERATION OF THE NATURAL COURSE OF ALLERGIC DISEASE

A fundamental objective in assessing the value and applicability of SCIT is to document its long-term efficacy and preventative capacity. Without long-term reduction in disease severity and disease modification after terminating treatment, immunotherapy may not be a viable alternative to pharmacological treatment due to cost and risk (20). Some studies indicate that the treatment may have a long-lasting effect. The PCDB study published by Durham et al (51) is a continuation of a previous study documenting efficacy SCIT (52). Patients with severe grass pollen rhinitis, uncontrolled by standard pharmacotherapy including topical glucocorticosteroids, were treated with preseasonal grass-SCIT and placebo. After less than one year of grass-SCIT, subjects experienced improved symptoms and a 60% reduction in the need for rescue medications. After three years of active treatment, subjects were rerandomized to continue with SCIT or to receive placebo. At the termination of the study, the symptom-medication scores between subjects continuing and discontinuing immunotherapy did not differ. Treated subjects, compared with a matched control group not receiving immunotherapy, had a >75% reduction in disease severity. An open study compared 13 patients, six years after having terminated a three-year course of grass pollen SCIT, with 10 patients of the control group who were not treated with SCIT (53). Clinical symptoms and the use of rescue drugs in the previously SCIT-treated subjects were significantly lower than in the control group. The patients were reevaluated after 12 years, and the beneficial effect of SCIT persisted (54). A retrospective, questionnaire-based evaluation compared SCIT-treated asthmatic subjects with dust mite or grass allergy with a matched control group approximately nine years after cessation of SCIT (55). The 48 SCIT-treated patients were three times less likely to experience asthmatic symptoms as the control group. However, asthma pharmacological therapy did not statistically differ between the two groups (55).

SAFETY

Injections of allergens into an IgE-sensitized patient always include a risk of inducing anaphylaxis. On the basis of the controlled studies included in the efficacy evaluation (Malling H-J, personal communication), 68% (44 out of 65) of studies in rhinitis and 72% (18 of 25) of studies in asthma reported systemic side effects. Anaphylactic shock, the clinically most important side effect, was observed in 6% (4 of 65) of rhinitis studies and 20% (5 of 25) of asthma studies. These data support the view that asthma is a separate risk factor for serious systemic side effects during SCIT (56) and also confirm the importance of the administration of SCIT as described in international recommendations (45,46).

INDICATION AND CONTRAINDICATIONS

When defining the indication for SCIT for inhalant allergies, it is advantageous to recognize that the allergen-IgE reaction results in a multiorgan disease, with symptoms in many patients occurring in the eyes, nose, and lungs (21). Some patients have symptoms predominantly from one organ, which does not indicate an absence of inflammation in other parts of the airways (25). Consequently, all symptoms should be considered when selecting the most appropriate treatment of the allergic disease (21). Before instituting immunotherapy, the following must be considered: (i) the severity and duration of symptoms, (ii) the requirement for and the effect of pharmaceutical therapy, (iii) the risk incurred by the treatment and the risk of the disease, (iv) psychological factors, and (v) the patient's attitude related to alleviating symptoms (drugs) versus interfering with the pathophysiological background of the disease (specific treatment).

The indication for allergen immunotherapy in allergic airway diseases relates to both the severity of the disease and the duration of the symptoms (20,21). Mild rhinitis symptoms that

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respond adequately to oral or topical antihistamines are not generally an indication for beginning SCIT. However, SCIT is a consideration if there is a need for repeated courses of topical glucocorticosteroids, both for a short or a long season, or symptoms lasting several months, even if these symptoms are rather mild and respond to pharmacological treatment (20).

In asthma, the number of drug doses needed to reduce symptoms, the frequency of daily administrations, and the number of organs needing treatment has an important influence on the rationale for initiating SCIT. SCIT offers the possibility of reducing the requirement for drugs and minimizing symptoms. It is a mistake to institute SCIT only in patients who do not respond to drug treatment or who develop side effects during drug treatment (20). Even though some guidelines recommend giving allergen SCIT only when all other forms of treatment fail, SCIT may be considered in patients with mild disease. Optimal results of SCIT are obtained in patients with mild disease, i.e., requiring a rather modest pharmacological treatment (34). The advantages of SCIT include minimizing medications, symptoms, and disease progression. The latter has not been achieved with pharmacological therapy.

Children probably respond better to immunotherapy than adults (20). Although this observation may relate to the chronological age of the patient, it is more likely related to the duration of the allergic disease. Attempts to interfere with the natural course of the disease should be introduced at a time when the patient has the capacity to respond positively, i.e., before the disease becomes a chronic, irreversible condition (57).

Risk-benefit assessments of both the allergic disease and treatment options are important for evaluating the indication for SCIT (20,21). The disabling nature of allergic rhinitis, which diminishes performance capacity in schoolwork, job, and social contacts, is of great importance for the affected subject's quality of life (58). Of additional concern is that a number of allergic rhinitis patients develop asthma during the course of their disease (59,60). Asthma is more severe than rhinitis in relation to acute attacks, hospital admissions, and possibly in days of missed work or school. Furthermore, asthma may develop into chronic, irreversible pulmonary impairment. Therefore, inadequate treatment may be associated with increased risk of remodeling and permanently decreased lung function (61,62). However, no treatment, including SCIT, has been proven to affect the risk of developing irreversible loss of lung function.

The hazards of SCIT are related to the risk of inducing anaphylaxis. The rate of severe, systemic reactions in patients with rhinitis treated with high potency vaccines is variable but is approximately 0.5% to 5% of the injections (63,64). Reactions are more likely during the induction phase but may occur at any time during the course of treatment (20). In asthma, the risk of systemic reactions is greater, primarily due to the increased possibility of bronchial obstruction. Consequently, it is advisable to monitor lung function before injections and to ensure optimal asthma pharmacotherapy during SCIT (20,21). Systemic reactions or anaphylaxis is a general limitation for the use of SCIT. Therefore, the decision to initiate SCIT and its administration should be directed by a specialist knowledgeable about these issues and prepared to treat anaphylaxis (20,21,45).

Psychological factors potentially affecting the decision to use SCIT include compliance with pharmacotherapy, concern of possible medication side effects, and the patient's perception of having a chronic disease with a continual need for medications. Studies of drug compliance or adherence in asthmatic patients show that only approximately half or less of the prescribed drugs are used (65,66). Drug compliance may be greater in rhinitis due to the usually shorter duration of symptoms in seasonal allergic rhinitis and recognition of drug efficacy due to more rapid or more evident symptom response (67). However, perennial, persistent, or chronic rhinitis is often the reason patients seek specialty care. These subjects are less likely to perceive symptom response with medications, making the likelihood of adherence lower due to the chronic nature of the therapy. It is important in treating allergic diseases to be aware of the patient's perception of disease severity, the psychological motivation associated with seeking care, the benefit or lack of benefit of prior pharmacotherapy, and the scientific understanding of the rationale for treating allergic inflammation.

Several aspects of the treatment of allergic rhinitis require careful consideration: (i) about 20% of subjects with rhinitis experience symptoms from the lower airways—often neither considered nor treated as asthma; (ii) patients with presenting symptoms only from the upper airways have a significant risk of developing asthma; (iii) patients with less intensive

Table 1 Considerations for Initiating Immunotherapy in Allergic Airway Diseases

1. IgE-mediated disease demonstrated by the presence of clinically significant positive skin tests and/or serum-specific IgE to relevant allergens
2. Specific allergen sensitivity responsible for clinical symptoms and the severity of disease
 - Confirmed by appearance of symptoms after natural exposure to allergens identified by allergy testing
 - Rarely confirmed by challenge with relevant allergens
3. Nonspecific triggers may play an additional, but only minimal, role in the induction of symptoms
4. Severity and duration of symptoms
 - Involvement of lower airways in patients with rhinitis
 - Increasing symptoms induced by succeeding seasons or perennial exposure
5. Inadequate response of symptoms to initial therapy
 - Response to allergen avoidance/reduction
 - Response to pharmacotherapy
6. Availability of standardized or high-quality allergen extracts ideal for preparation of vaccines for immunotherapy
7. Ideally clinical efficacy and safety of immunotherapy with selected allergens confirmed by randomized placebo-controlled, double-blind studies
8. Psychological and social considerations
 - Cost of pharmacotherapy and immunotherapy
 - Patient comfort level with pharmacotherapy side effects or potential side effects
 - Impaired quality of life despite adequate pharmacotherapy
 - Concern about prevention of long-term disease progression
9. No relative contraindications

Source: Adapted from Refs. 20, 21.

Table 2 General Indications for Immunotherapy in Allergic Airway Diseases

- Patients with symptoms induced predominantly by allergen exposure that cannot be avoided
- Patients with a prolonged season or with increasing symptoms induced by succeeding pollen seasons
- Rhinitis associated with symptoms from the lower airways during peak allergen exposure
- Patients with insufficient symptom control with pharmacotherapy
- Patients who do not wish to be on constant or long-term pharmacotherapy
- Patients with undesirable side effects with pharmacotherapy

symptoms need less symptomatic treatment, but intervention affecting the natural course of the disease is more successful. There are no definite rules for the institution of SCIT in allergic rhinitis or asthma. The initiation of SCIT is based on a careful balancing of advantages and disadvantages, taking into consideration the patient's attitude to both the symptoms and possible treatments of the disease (20). Analyzed in this way, SCIT is not considered to be the ultimate treatment but, instead, is a supplement to pharmacotherapy in the early phase of the disease (20,21). The considerations for initiating immunotherapy in allergic rhinitis and asthma are illustrated in Table 1 and the indications in Table 2 (3,20,21,45). The complexity of these decisions support the practice standard of knowledgeable specialists being involved in the decision rather than remote testing services or vaccine vendors.

Contraindications

In contrast to the multiple factors defining the indications for SCIT, the contraindications are more straightforward (20,21). Relative contraindications involve serious immunopathological or immunodeficiency diseases including some forms of malignancy or cancer treatment (in the European guidelines any malignancy is an absolute contraindication), significant cardiovascular diseases (due to the risk of hypotension and the potential administration of epinephrine), treatment with β -blockers (reduces the effectiveness of epinephrine in the treatment of

anaphylaxis), severe asthma uncontrolled by pharmacotherapy and irreversible airway obstruction defined as FEV₁ consistently <70% of predicted value in spite of adequate drug treatment, severe psychological disorders, and low probability of compliance. Other relative contraindications include initiating SCIT during pregnancy due to the risk of anaphylaxis for the mother and possible associated detrimental effect on the fetus. Well-tolerated and effective SCIT may be continued if pregnancy occurs after a woman has received immunotherapy for several months. Age is a relative contraindication. In children less than five years of age, SCIT with inhalant allergens is less commonly utilized because of less evidence or proof of the role of inhalation allergens in the total manifestations of disease, because of the fact that some infants improve with growth, and because of the difficulty in recognizing systemic reactions in very young children. In patients >50 years of age, allergy may not be as important in the development of symptoms and there are limited data demonstrating efficacy. However, in appropriate adults older than 50 years of age, SCIT is a reasonable consideration (20,21).

SCIT should be prescribed by specialists and administered by physicians familiar with this special treatment and capable of treating anaphylaxis (21,45). The recommended equipment for settings where SCIT is administered includes epinephrine for injection; equipment for administering intravenous fluids and oxygen, including an oral airway; equipment for monitoring blood pressure; and pharmacological agents, including glucocorticosteroids, antihistamines, and vasopressors for injection (20,21). When SCIT is administered remote from emergency care access, additional rescue equipment may be appropriate. However, the most important recommendation is the prompt recognition of systemic reactions or anaphylaxis and the immediate administration of epinephrine.

DURATION OF IMMUNOTHERAPY

The international guidelines recommend perennial treatment because it attains a higher cumulative allergen dose while reducing the side effects that are a problem predominantly during the induction phase (20,21). Injection of a significant maximum allergen dose, in the range 5 to 20 µg of the major allergen, is associated with symptom-reduction efficacy and possibly disease modification with improvement persisting after discontinuation. Because there may be poorer patient compliance with perennial treatment, several short-term immunotherapy studies have been published (68,69). The problem with this design is that the preseasonal, 7-injection regimen results in low-dose immunotherapy because of a low cumulative allergen dose, and consequently, the level of efficacy obtained is only during the allergen season immediately following the preseasonal treatment. The immunological changes do not accomplish a fundamental change in the allergic phenotype. This form of treatment is comparable to symptomatic drug treatments that suppress the clinical symptoms while being administered but do not modify the long-term disease. From a cost-effectiveness perspective, SCIT, without documented long-term efficacy and preventive capacity, is less attractive, especially when considering the potential risk of inducing anaphylaxis. A perennial maintenance regimen using depot-allergen vaccines, administered six times per year (an interval of 8 weeks between injections) reduces the total number of injections, provides considerably higher doses of allergen, and minimizes risks compared with aqueous vaccines (56).

DISCONTINUATION OF IMMUNOTHERAPY

SCIT is usually administered for a defined time, typically three to five years. Efficacy is normally manifest after one year of treatment. If no improvement is observed after two years of treatment, the probability of obtaining efficacy is low and SCIT generally should be terminated (20,45). Short-term treatment has no protracted effect after SCIT is discontinued. The recommendation for a minimum of three years of maintenance SCIT is based on the observation that discontinuing SCIT after less than three years results in a higher relapse rate (70,71). Given the relatively slow onset of action and the knowledge of the likely immune mechanisms, there is a tendency toward extending the treatment period to five years, as is now commonly used for venom allergy. This is not based on scientific data obtained but is proposed in an attempt to

reduce the risk of reoccurrence of symptoms. In patients who improve with SCIT and deteriorate following discontinuation, the course of SCIT should probably be prolonged. In nonresponders, i.e., patients showing marginal or no efficacy after one year of treatment or 18 months in subjects with a major seasonal component, the indication for SCIT should be carefully reassessed with the view of determining whether allergy due to the identified allergens is responsible for the persisting symptoms (20). Patients not benefiting from SCIT usually should be discontinued after no more than two years of treatment at the optimal dose or consideration given to alternative allergens contributing to symptoms. Likewise, in patients experiencing severe anaphylaxis with SCIT, considerations should be given to alternative treatments. Nonadherence or limitations imposed by travel or scheduling would also be indications for discontinuation (45,72).

DISEASE PREVENTION WITH ALLERGEN IMMUNOTHERAPY

The capacity of SCIT to reduce the risk of developing new sensitizations was suggested by two large-scale studies in patients sensitized to one allergen only (73,74). The Purello-D'Ambrosio et al. (73) study followed for three years after SCIT, in an open retrospective design, 7182 originally monosensitized (to a variety of allergens) children treated with SCIT for four years (total of 7 years of observation). The control group consisted of 1214 comparable patients followed for seven years. The development of sensitization to new allergens at the five-year follow-up (two years after stopping SCIT) was 68% in the control group versus 24% in the SCIT group. Corresponding figures at the seven-year follow-up (4 years after stopping SCIT) were 78% and 27%, respectively. The difference between the control group and SCIT-treated group is statistically and clinically convincing. The Pajno et al. (74) study followed 75 SCIT-treated children, monosensitized to house dust mites, and 63 comparable controls treated pharmacologically for six years. The results show that 74% in the SCIT-treated group versus 33% in the control group remained monosensitized (specific IgE to only one allergen).

Likewise, SCIT as a prevention for progression of rhinitis into asthma has been suggested in studies. A multicenter trial, the Preventive Allergy Treatment Study, investigated the capacity of SCIT of allergic rhinitis to prevent the disease progressing into asthma (75). Children with allergy to birch and grass pollens, without clinical evidence of lower airway BHR, were randomized to receive either SCIT or optimal pharmacotherapy. After three years of treatment, the number of patients developing clinical asthma was statistically reduced in the SCIT group (24%) versus the pharmacotherapy group (44%). These data demonstrate the clinically important risk of developing lower airway symptoms in subjects with allergic rhinitis and demonstrate risk reduction with SCIT. Two years after terminating SCIT (5-year follow-up) (76) and seven years after discontinuing SCIT (10-year follow-up) (77), the beneficial effect of SCIT persisted (Fig. 4). Asthma prevention not only occurred with seasonal (pollen-induced)

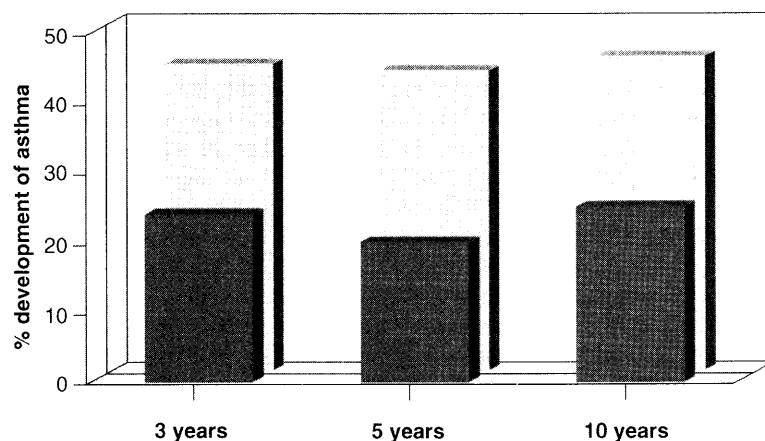


Figure 4 Frequency of the development of asthma in SCIT-treated children (dark grey) and controls (light grey) at discontinuation of immunotherapy (3 years), two years after termination (5 years total) and seven years after termination (10 years total). Source: From Ref. 77.

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asthma but also with perennial asthma. Furthermore, the study showed that careful evaluation for asthma uncovered 20% of unidentified mild seasonal asthma in the 205 children recruited for rhinitis and more than one-third of the subjects with rhinitis had seasonal BHR measured by methacholine challenge (75). BHR to methacholine decreased significantly in SCIT-treated patients. However, only 2 out of 40 patients with asthma at inclusion were free of asthma after three years, indicating that SCIT has a greater capacity for asthma prevention than remission.

SALIENT POINTS

- The benefits of allergen immunotherapy for allergic rhinitis and asthma are well documented and based on PCDB studies with an appropriate number of carefully selected patients and the use of potent, well-characterized allergen vaccines at sufficient dosage.
- In clinical practice, immunotherapy ideally should be performed with allergen vaccines, which in clinical trials have demonstrated clinical efficacy and safety.
- The magnitude of clinical efficacy as assessed by symptom reduction is equivalent to or better than results obtained with optimal pharmacotherapy.
- The advantage of immunotherapy compared with pharmacotherapy is the capacity to reduce symptoms and simultaneously reduce the need for medications and potentially improve the natural course of the disease. The result is improved clinical outcomes with SCIT and reduction of progression into more severe disease.
- Allergen-specific immunotherapy is the only treatment that may alter the natural course of the disease with documented long-term efficacy and modulation of disease progression after termination of the treatment.
- Immunotherapy should be introduced at a time when the patient has the capacity to respond positively, i.e., before the disease becomes chronic or irreversible. Immunotherapy does not replace pharmacotherapy but complements or supplements if used in the early phase of allergic disease.
- Candidates for immunotherapy are subjects with rhinitis and/or asthma, symptoms induced by allergens and limited evidence of irreversible, structural airway changes. Age may affect response with younger subjects generally responding better than older individuals.
- Perennial SCIT is the only treatment in severe allergic rhinitis documented to reduce the development of asthma.
- Immunotherapy ideally should be continued for at least three, and probably five years, to achieve long-term, persistent clinical efficacy.

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