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Review Article

# Specific immunotherapy for allergic diseases

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Specific allergen immunotherapy (SIT) involves the administration of allergen extracts to modify or abolish symptoms associated with atopic allergy. The process is specific, in that the treatment is targeted at those allergens recognized by the patient and physician as responsible for symptoms. A decision to use SIT therefore demands a careful assessment of the patient's condition and the role of allergic triggers. Immunotherapy was first developed at St Mary's Hospital, London at the end of the 19th century,[1] and many of the basic principles remain valid today.

Usually, patients receive a course of injections, starting with a very low dose of allergen, increased gradually to achieve a plateau or maintenance dose. Maintenance injections are then given at 4-6 weekly intervals for 2 to 3 years. The up-dosing phase is generally given as a series of weekly injections, but several alternative induction regimens have been tried; some give several doses on each day then wait a week before giving further series of injections (semi-rush protocol), while others give the whole series of incremental injections in a single day (rush protocol). The main drawback to these rapid up-dosing regimens is the risk of adverse reactions, which is much higher than that in conventional protocols. On the other hand, full protection can be attained in a few days instead of the three months required in the conventional regime. This may be particularly useful in patients being treated for life-threatening conditions such as anaphylaxis induced by hymenoptera stings.

With the increasing trend towards evidence-based practice, allergists have been challenged to provide data to support their use of SIT. While many older studies were of doubtful quality, recent clinical trials have confirmed the usefulness of SIT as a treatment for allergic rhinitis and hypersensitivity to wasp and bee venom. The value of SIT as a primary treatment for asthma has, however, been more controversial.

## Mechanisms of immunotherapy

Several mechanisms have been proposed to explain the beneficial effects of immunotherapy **(Table 1).**

**TABLE 1.** POSSIBLE MECHANISMS OF IMMUNOTHERAPY

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| Induction of IgG (blocking) antibodies |
| Reduction in specific IgE (long-term) |
| Reduced recruitment of effector cells |
| Altered T-cell cytokine balance (shift to Th1 from Th2) |
| Th2 cell anergy |
| Induction of regulatory T cells |

In previous studies, SIT was thought to produce an effect on allergen-specific antibodies. Allergen-specific immunoglobulin (Ig) E levels rise temporarily during the initial phase of SIT, but fall back to pre-

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treatment levels during maintenance therapy.[2] The immediate skin test response can be reduced after SIT, but this effect is relatively small compared to the degree of clinical benefit. In contrast, the late-phase skin test response is virtually abolished after successful SIT. Similar patterns are observed for late-phase nasal and airway responses.[3] SIT also induces allergen-specific IgG antibodies, an observation that led to suggestions that antibodies might intercept the allergen and impede allergic response. Current opinion is against this, partly because many mast cells are on the mucosal surfaces, and therefore meet allergens before antibodies could interpose themselves and partly because the rise in IgG follows rather than precedes the onset of clinical benefit. Moreover, there is a poor correlation between the amount of allergen-specific IgG and clinical protection. IgG mainly correlates with the dose of allergen that has been given. It is true that in patients treated for venom anaphylaxis, the development of allergen-specific IgG antibody correlates with clinical efficacy but for other allergens, the magnitude of the IgG response is unrelated to the degree of efficacy.

Allergen-specific T-cell responses are also affected by SIT. Both in the skin and in the nose, successful SIT is accompanied by a reduction in T-cell and eosinophil recruitment in response to allergen challenge. In parallel, there is a shift in the balance of T helper 1 (Th1) and Th2 cytokine expression in the allergen-challenged site. Th2 cytokine expression is not affected but there is an increased proportion of T-cells expressing the Th1 cytokines interleukin-2 (IL-2), interferon-gamma (IFN-$\gamma$), and IL-12.[4-6] After venom SIT; there is induction of regulatory T cells, producing IL-10 as well as a shift in Th1:Th2 balance.[7,8] Similar findings have also been reported following SIT with inhalant allergens.[8,9] A study in Indonesia indicated that SIT suppresses IL-4 and IL-5 and elevates IL-2 and IFN-$\gamma$. A very important finding in this study is that long-term use of corticosteroid inhalation yields more suppression to IL-5, resulting in the modulation of immune response which then increases IL-2 and causes improvement of clinical manifestations represented by the improvement of FEV-1 reversibility.[10] IL-10 has a complex series of actions on the immune response, including stimulating production of the $IgG_4$ subclass, which may therefore rise as an indicator of the beneficial effect, rather than as a direct player in the mechanism of SIT.[11] A study from Spain indicated evidence of Th2 apoptosis as a basic mechanism of SIT. The study was performed in lymphocytes from normal subjects and atopic patients, some of whom were treated with SIT. Cells were cultured in the presence of gramineous pollen (*Lolium perenne*) allergenic extracts. Cell phenotype, intracellular cytokine expression, and apoptosis were measured. The results of this study showed that allergens induced apoptosis of lymphocytes in SIT-treated atopic patients. Apoptosis occured mainly in Th2 lymphocytes with the IL-$4^+$/$CD4^+$ phenotype and subsequently increased the percentage of IFN-$g^+$ cells in the culture. The authors suggested that the shift from Th2 to Th1 induced by SIT in atopic patients may be mediated, at least in part, by the induction of an activation-induced cell death process in allergen responder Th2 cells.[12]

Concurrently, these findings suggest that SIT has a modulatory effect on allergen-specific T cells. This helps to explain why the clinical and late-phase responses are attenuated without such a large effect on allergen-specific antibody levels.

## SIT for venom hypersensitivity

Anaphylaxis to hymenoptera venom is relatively rare, but can be fatal. Venom-specific IgE antibodies can be found in 30-40% of adults for a few months following a sting, but these usually disappear in a few months. This response is related to total serum IgE and the patient's IgE response to inhalant allergens. Some unlucky individuals react more vigorously with high concentrations of venom-specific antibodies, which may persist for many years without further exposure to stings. It is this group of patients that are at risk for anaphylaxis to subsequent stings and a small number die from anaphylaxis each year. Estimates are hard to come by, but a figure of 10 to 20 deaths per year in the USA has been cited. This problem should not be confused with deaths from "killer bees," which are a subspecies that is behaviorally inclined to deliver multiple stings. The bees are enraged by scent of venom, and so once one insect has stung, other bees in the neighborhood will attack. Death is caused by massive envenomation and not by any allergic or immunological process.

The decision to give venom immunotherapy should be based on careful assessment of the patient,

as well as an understanding of the natural history of venom allergy.[13] Patients who have experienced systemic symptoms after a sting are at much greater risk of anaphylaxis on subsequent stings, as compared to patients who have only had large local reactions. The frequency of systemic reactions to stings in children and adults with a history of large local reactions is about 5% to 10%, whereas the risk in patients with previous systemic reactions is between 30% and 70%. In general, children are less at risk for repeated systemic reactions compared to those with a history of milder reactions. With time, the risk of a systemic reaction decreases; by ten years after a previous systemic response, the risk is about 15%, compared to the general population risk of 2% to 3%. Occupational and geographic factors that may affect the likelihood of future stings should also be considered. Bee stings are much more common in beekeepers, their families, and neighbors, while wasp stings tend to be sporadic, yet an occupational hazard for bakers and greengrocers. Other factors to consider are the potential risks of emergency treatment with epinephrine and the various medical contraindications to SIT.

The introduction of pure venom preparations for SIT has led to a substantial improvement in the effectiveness of SIT for venom allergy. Older preparations with whole body extracts were no more effective than placebo. Desensitization with venom extracts accelerates the rate at which the risk decreases and rapidly provides protection against field and laboratory stings. After completing venom SIT, there is a residual risk of systemic reactions of approximately 10%, but when reactions do occur after SIT, they are typically mild. Patients who receive SIT should be supplied with anti-allergic medication for use in the event of a sting during or after therapy. Some allergists recommend providing adrenaline injection during therapy, but this is not generally considered necessary once the patient has reached the maintenance dose of SIT.

## SIT for allergic rhinitis

SIT is a useful treatment for allergic rhinitis, especially when the range of allergens responsible is narrow. As with other uses of SIT, it is important to select patients appropriately. The allergic basis of rhinitis should be carefully assessed both on history and on skin tests or blood tests, and other causes of nasal symptoms should be excluded. Direct challenge tests, for assessing nasal sensitivity to allergen, are not used in routine clinical practice but may be useful for assessing effectiveness in clinical trials. The most difficult group to assess is patients with persistent non-seasonal rhinitis, who have small positive skin tests to house dust mites. In this group it can be extremely difficult to recognize whether the patient has symptoms related to house dust mite, or whether they have non-allergic rhinitis and just happen to be sensitized to an allergen that is not clinically relevant. This difficulty in being certain about clinical relevance contributes to the apparently lower degree of efficacy found with house dust mite SIT.

The effectiveness of SIT in intermittent (seasonal) allergic rhinitis has been confirmed by many trials, using grass, ragweed, and birch pollen extracts. Importantly, SIT has shown to be effective even in patients with severe seasonal rhinitis resistant to conventional drug therapy.[14] Limited data are available regarding the long-term efficacy of rhinitis, but there are data indicating that three years in therapy is sufficient to give lasting benefit, and the effects appear to persist for at least six years after discontinuing therapy.[15] This statement is in contrast with conventional drugs, whose effects usually wear off very soon after discontinuing therapy. Other studies have shown that one year's treatment is insufficient to give lasting benefit.[16] The benefits of SIT for perennial rhinitis are less than for seasonal rhinitis. In part, this reflects the difficulty in determining the extent to which allergy is responsible for perennial symptoms. Allergy to house dust mites is common and does not always cause symptoms. Conversely, there are other causes of perennial rhinitis including vasomotor instability, infection, aspirin sensitivity, etc. Nevertheless, clinical trials have shown a definite benefit in appropriately selected subjects. Clearer evidence has been obtained in rhinitis due to pet allergy. Several studies have shown a marked improvement in the tolerance of cat exposure after SIT, confirmed both on challenge tests and simulated natural exposure.[17]

As with any therapy, the risks and cost-effectiveness of SIT need to be assessed on a case-by-case basis. Current drug therapy for rhinitis can be very effective, but a significant proportion of rhinitis patients

experience nose bleeds from intranasal steroids and drowsiness from their antihistamines. Others find pharmacotherapy inconvenient or ineffective. Moreover, we are now more aware of the adverse effects of rhinitis on quality of life. SIT offers a useful option for these patients, as well as a logical approach to dealing with the underlying problem.

## SIT for asthma

Immunotherapy has been widely used to treat allergic asthma, although the introduction of effective inhaled therapies has changed the general pattern of asthma care. Concern over adverse reactions, including a small number of fatalities, has led some countries to restrict the use of SIT for asthma treatment, although asthma remains a common indication for SIT in many parts of North America and continental Europe.[18,19]

Current drug therapies for asthma suppress airway inflammation and relieve bronchospasm. None of these treatments are curative and asthma recurs rapidly on ceasing treatment. Allergen avoidance can help in those with allergic asthma, but while extreme forms of allergen avoidance (e.g., admission to hospital, sending children to holiday homes at altitude) can improve asthma control, there is less evidence for benefit with the degree of allergen avoidance that can be achieved in suburban homes. Thus, there is scope for improving asthma care and for identifying allergen-specific therapies. SIT offers the possibility of deviating the immune response away from the allergic pattern and towards a more protective or less damaging response. However, SIT remains controversial as a treatment for asthma because of the potential side effects.

The efficacy of SIT in adult asthma has been assessed in many trials over the last 50 years. Some of these studies have been difficult to interpret, since either poor quality allergen extracts were used or the studies were poorly designed. A meta-analysis of all trials published between 1954 and 1998 found clear evidence for the beneficial effects of SIT in asthma.[19] Symptom scores were reported in 22 trials and overall there was a small but definite improvement in those groups treated with mite SIT or pollen SIT, compared to the placebo-treated groups. There was a parallel reduction in asthma medication usage but no improvement in lung function measurements. However, SIT did reduce the airways response to inhalation of specific allergen.

Three double-blind placebo-controlled (DBPC) studies have found that SIT has a beneficial effect in patients with grass pollen asthma as assessed by a reduction in asthma symptom and treatment scores. Active treatment led to a 60% to 75% reduction in symptom scores as compared to placebo-treated patients. Failure of 24% was reported using house extract in the treatment of mild asthma in children, and an addition of budesonide inhalation resulted 100% improvement in the term of FEV-1 reversibility.[10] An important recent study of SIT for ragweed allergy found that patients who received active injections had an improvement in peak flow rates during the pollen season as well as reduced hay fever symptoms and reduced sensitivity to laboratory challenge with ragweed pollen extracts.[20] In addition, the active group required much less anti-asthma medication. However, the parallel economic analysis indicated that the cost-saving asthma drugs were less than the costs of SIT.

In asthmatic patients sensitive to cats, SIT reduces both the early asthmatic response to inhaled allergen and responses to simulated natural exposure in a "cat room." Interestingly, there was no protection against allergen-induced increases in nonspecific bronchial hyper responsiveness, despite the clear delay in the onset of symptoms and an overall reduction in symptoms and peak flow recordings after exposure to cats. Others have found reductions in both specific and non-specific bronchial reactivity after SIT for cat allergy (measured by inhalation challenges with cat extract and histamine respectively).[21]

## Comparison of SIT with other types of treatment for asthma

The majority of clinical trials of SIT for asthma have compared SIT either with historical controls or with a matched placebo-treated group. To this date, the effectiveness of specific SIT in asthma has rarely been compared with conventional management (with avoidance measures and conventional inhaled or oral drugs). One recent study assessed SIT in asthmatic children receiving conventional drug therapy and found no additional benefit in patients who were

already receiving optimal drug therapy.[22] There are some significant criticisms of this study and further work of this type is urgently needed. It is also important that trials include analysis of cost-benefit and cost-effectiveness, since purchasers of health care are increasingly demanding this evidence before agreeing to fund therapies.

## Effects on natural history of allergic disease

A proportion of patients with allergic rhinitis develop asthma each year. It has been suggested that SIT may modify the natural history of asthma in children who are known to be atopic but have not yet developed asthma. During the 1960s and 1970s, the annual rate of progression was estimated at 5% in college students,[23] but this figure has not been updated. An early open study using uncharacterized mixed allergen extracts suggested that SIT may increase the rate of remission for children with asthma and may also reduce the severity of symptoms in those who remain symptomatic.[24] Further evidence that SIT can modify the natural history of allergic disease has emerged in studies showing that the SIT reduces the probability of developing new sensitivities (to allergens other than the one used for therapy).[25] A major multicenter study is assessing whether SIT is able to prevent allergic children aged 7-13 years from developing asthma. After 3 years of therapy, 28% fewer children had asthma symptoms compared with the control group, suggesting that SIT is making a real difference to the outcome of allergic sensitization. A critical question is whether SIT postpones the onset of asthma or prevents it completely; however, the answer will not emerge from the study for several years.[26] In contrast, there is no current evidence that SIT influences the evolution of established asthma. Studies that have investigated withdrawal of therapy have found rapid recurrence of asthma symptoms, although rhinitis symptoms seem to show much more sustained relief after SIT.[27]

Thus SIT is a valid but controversial treatment for asthma. While it seems entirely logical to try to treat allergic disorders by specifically suppressing the immune response to the triggering agents, the critical issue is whether SIT in its present form is the best option for managing patients with asthma. Assessment requires proper comparisons of best current SIT versus best current drug therapy, with robust endpoints including symptoms, objective measures of lung function, evaluation of cost-benefit ratios, safety, and quality of life. In vitro and in vivo measures such as skin test responses or allergen-specific IgG4 measurements are not sufficiently specific or sensitive to serve as surrogates for clinical efficacy. To date there have been relatively few well-controlled studies of SIT in asthma but there is increasing evidence that SIT is beneficial in mite-induced and pollen-induced asthma. The clinical efficacy of SIT in adult asthmatic patients sensitive to cats or molds is less certain, and no comparative studies with conventional treatment have been performed. Further clinical trials are indicated, particularly in mild to moderate childhood asthma and also in patients with atopic disease who have not yet developed asthma but are at high risk of progression to asthma.

## Safety of SIT

The main factor cited against the widespread adoption of SIT for asthma is the risk of serious adverse reactions. In the UK between 1957 and 1986, 26 fatal reactions due to SIT were reported to the Committee on Safety of Medicines.[28] In 17 of the fatal cases, the indication for SIT were documented: 16 of these 17 patients were receiving SIT to treat asthma. Similarly, in the American Academy of Allergy, Asthma, and Immunology's confidential inquiry into SIT-associated deaths, asthma appeared to be in virtually all the fatal cases.[29] In those where asthma was not cited as a contributory factor, documentation of asthma status was missing and certainly bronchospasm was a cardinal feature of the clinical course of the anaphylactic reactions. The incidence of systemic reactions in patients receiving SIT for asthma varies between series and has been reported to range from 5% to 35%. Study in Surabaya, in childhood asthma showed no systemic and local side effects.[10] The central issue in using safety as an endpoint is to recognize that all treatments carry risks. Where differential risks exist between therapies, a more risky therapy can only be justified if that therapy offers substantial additional benefit over the safer therapy. The science of assessing risk-benefit ratios is still in its infancy and we have to recognize that even when faced with the same facts, different

patients and agencies can come to widely varying risk assessments.

Separately, it is generally agreed that immunomodulatory treatments should not be used in patients with autoimmune disorders or malignant disease. While there is no hard evidence that SIT is actually harmful in these groups, conservative opinion is that it seems unwise to attempt manipulation of the immune system in such patients, since the risk that spontaneous and unrelated variations in the autoimmune disorder or cancer may be blamed on SIT. However, provided the risks and benefits are weighed up and discussed with the patient, SIT may be given where the risk-benefit ratio is overwhelmingly in favor of treatment. Other medical contraindications to SIT include the coexistence of significant cardiac disease, which may be exacerbated by any adverse reactions to SIT. Beta-blockers are also contraindicated in patients receiving SIT. Although they do not increase the risk of adverse reactions, they will prevent the patient from responding to epinephrine, which may be needed to treat adverse reactions to SIT. Where the indication for SIT is strong, alternatives to beta-blockers should be used, so that the SIT can be given safely.

## Alternative forms of immunotherapy

Alternative allergy practice covers three principal themes: The use of unconventional diagnostic tests to seek causative agents for diseases that everyone agrees are allergic in origin, the use of unconventional therapies to treat allergic disease, and the diagnosis and therapy of diseases which are not conventionally considered to involve allergic mechanisms. Alternative immunotherapy regimes fall into the second of these categories, but the other two areas fall outside the scope of this review.

Several unconventional forms of immunotherapy have been described and tested, including the use of topical immunotherapy, enzyme-potentiated desensitization and homeopathic desensitization.

## Topical immunotherapy

High-dose topical immunotherapy regimes were used in the first half of the 20th century, but subsequently fell into disrepute. The last decade has seen a revival of interest in sublingual immunotherapy, which is based on the concept that allergens given via the mucosal surface are handled differently from allergens given by injection. Low dose sub-lingual immunotherapy has been studied in Surabaya, and resulted the in improvement of clinical symptom as indicated by improvement of PEFR variability.[30] In animal models, IgE responses to allergens can be reduced or prevented by oral administration of allergen, and there are several supportive clinical trials in man.

The precise mechanisms by which this "oral tolerance" is induced remains unclear, but it seems likely that the route of allergen processing and presentation is a critical determinant of the subsequent T-cell response. In mice, locally administered allergen is taken up by mucosal dendritic cells and then presented to T cells together with IL-12, biasing the response towards a Th1 profile and away from the pro-IgE Th2 profile. It is less clear whether this mechanism can suppress established allergic responses. In contrast to the animal models, the immunological response to sublingual SIT has been relatively modest in human studies. Some changes have been found in skin sensitivity, but most studies have not found any change in allergen-specific IgE, allergen-specific IgG, or T-cell cytokines. The 1998 European Academy of Allergy and Clinical Immunology (EAACI) review on local immunotherapy,[31] identified 31 published studies: 14 used the nasal route, 9 used the oral route, 6 used the sublingual route, and 2 gave the allergen directly into the airways. Most of these studies were quite small, and various different methodologies had been used, but by careful meta-analysis, some conclusions could be drawn. First, it was apparent that nasal immunotherapy was effective with a benefit found in 13 out of 14 studies. The benefits of nasal SIT appear to be sustained only while the therapy was continued: After 2 years of successful therapy, the level of symptoms in the subsequent season was similar to untreated patients. Local side effects were common, and it is arguable that nasal immunotherapy might be working by causing repeated degranulation of local mast cells, and subsequent local tolerance of allergic inflammation, rather than through a true immunological effect. In contrast to the sublingual route, oral immunotherapy seems to be ineffective. Only 6 eligible studies of sublingual SIT were identified, with 4

in adults and 2 in children. A total of 117 patients received active therapy in these studies. All 6 studies found a benefit for active therapy, and all 6 studies used the sublingual-swallow method (i.e., the extract was placed under the tongue, held there for a period of minutes, and then swallowed).[32] Systemic side effects were relatively rare, and none of the side effects were judged to be life threatening. A significant reduction in skin test reactivity was found in one study, but there were no measurable changes in bronchial responsiveness to allergen or to methacholine.

The EAACI position paper concluded that sublingual immunotherapy has been shown to be efficacious in patients with rhinitis, but insufficient information was available to draw any conclusions for its use in asthma. Several further studies have been published since 1999, most of which appear to show some benefit on nasal symptoms, albeit to a lesser degree than is found with standard SIT. Despite claims from some proponents and manufacturers, the general view is that it is still too early to recommend sublingual SIT as a viable alternative to conventional injection SIT.

## Conclusions

SIT has been in use for over a century and is clinically effective in patients with rhinitis or asthma whose symptoms are clearly driven by allergic triggers. It is perhaps surprising that we are only now beginning to understand how SIT works, but the general view is that the vaccination protocol induces regulatory T cells that dampen the response to allergen exposure in sensitized subjects. When used in appropriately selected patients, SIT is effective and safe, but care is needed to recognize and treat adverse reactions. As well as careful patient selection, appropriate training of allergists and SIT clinic support staff is essential.

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