Allergen immunotherapy

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Specific immunotherapy (SIT) involves the administration of allergen extracts to achieve clinical tolerance of those allergens that cause symptoms in patients with allergic conditions. Immunotherapy is effective in patients with mild forms of allergic disease and also in those who do not respond well to standard drug therapy. Most SIT is given by means of injection, but there is increasing interest in performing SIT through the sublingual route. SIT remains the treatment of choice for patients with systemic allergic reactions to wasp and bee stings and should be considered as an option in patients with allergic rhinitis, asthma, or both. SIT can modify the course of allergic disease by reducing the risk of new allergic sensitizations and inhibiting the development of clinical asthma in children treated for allergic rhinitis. The precise mechanisms responsible for the beneficial effects of SIT remain a matter of research and debate. An effect on regulatory T cells seems most probable and is associated with switching of allergen-specific B cells toward IgG4 production. Few direct comparisons of SIT and drug therapy have been made. Existing data suggest that the effects of SIT take longer to develop, but once established, SIT achieves long-lasting relief of allergic symptoms, whereas the benefits of drugs only last as long as they are continued. (J Allergy Clin Immunol 2010;125:S306-13.)

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In allergen specific immunotherapy (SIT) allergen extracts are given to patients with allergic conditions to modify or abolish their symptoms. The process is specific in that SIT targets those allergens identified by the patient and physician as responsible for symptoms. Although the precise mechanisms involved remain uncertain, there is a substantial body of clinical evidence and practice to support the use of SIT. Before deciding to use SIT, the patient's condition needs to be carefully assessed, with particular regard to allergic triggers. In addition, because the course of treatment is lengthy and relatively expensive, there must also be an assessment of the risks and costs compared with those of symptomatic treatment with antihistamines and topical corticosteroids.

Abbreviations used
EPD: Enzyme-potentiated desensitization
SIT: Specific immunotherapy
SLIT: Sublingual immunotherapy
VIT: Venom immunotherapy

Immunotherapy was first developed at St Mary's Hospital London at the end of the 19th century,[1] and many of the basic principles described by Noon and Freeman remain valid today. However, over the years, SIT has evolved in different ways in different centers and in different countries, leading to varied treatment regimens and distinct philosophic approaches to the therapy. Indeed, much of the early literature on SIT is striking for its clinical empiricism and the lack of the type of objective evidence that would be required if this technique were to be introduced nowadays. Unfortunately, this has allowed critics to level charges of unscientific practice against allergists, even though the same point could be made about a whole range of medical practice. In recent years, clinical trials conducted according to modern principles have confirmed the effectiveness of SIT and have validated several of the alternative regimens that have been tried over the years. However, there is still a range of clinical practice and a variety of strongly held opinion about the best way to perform SIT. In particular, American allergists tend to treat for all sensitivities identified as clinically relevant on skin testing using mixtures of extracts prepared from bulk vials, whereas in Europe patients are normally only treated with a single allergen, which is supplied direct from the manufacturer. Mixed allergen extracts are available and used in some parts of Europe but only as custom mixes from manufacturers. Another difference in clinical practice is that allergen extracts used in the United States are prepared in the allergist's office, whereas those used in Europe are usually supplied by the manufacturer in their final form. European extracts are dialyzed to remove low-molecular-weight components and standardized according to their ability to elicit a wheal. In the United States extracts might not be dialyzed; although ragweed and cat extracts are standardized in terms of major allergen content, most extracts are standardized by their ability to elicit erythema rather than wheal. However, at the end of the day, the basic aims and principles of SIT are similar worldwide: the differences are in the details.

Typically, patients receive a course of injections, starting with a very low dose of allergen and building up gradually until a plateau or maintenance dose is achieved. Maintenance injections are then given at 4- to 6-week intervals for 3 to 5 years. The updosing phase is generally given as a series of weekly injections, but several alternative induction regimens have been tried, some giving several doses on each day and then waiting a week before giving a further series of injections (cluster protocol), whereas others give the whole series of incremental injections in a single day (rush protocol). The main drawback to the rush protocol is the risk of adverse reactions, which are much more common than in conventional or cluster protocols. On the other hand, full

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protection against anaphylaxis induced by Hymenoptera stings can be attained in a few days compared with the 3 months required with the conventional regimen.

MECHANISMS OF IMMUNOTHERAPY

The primary reason for studying the mechanisms of SIT is to seek out the element or elements that are biologically important and hence devise new forms of immunotherapy that might improve efficacy, increase safety margins, shorten treatment courses, or achieve more durable results. Several mechanisms have been proposed to explain the beneficial effects of immunotherapy (Table I). Whether administered by means of injection or sublingually, SIT induces changes in T-cell and antibody responses. The challenge for clinical scientists has been to work out which of the observed changes drive the clinical benefit and which are just epiphenomena. Allergen-specific IgE levels increase temporarily during the initial phase of SIT but fall back to pretreatment levels during maintenance therapy.[2] The immediate wheal-and-flare response to skin testing usually reduces during the initial phases of SIT, but this effect is relatively small compared with the degree of clinical benefit. In contrast, the late-phase response to skin testing is virtually abolished after successful SIT. Similar patterns are observed for late-phase responses in the nose and airways.[3] SIT also induces allergen-specific IgG antibodies, particularly antibodies of the IgG4 subclass. At one time, it was believed that these antibodies might intercept the allergenic particles at the mucosal surface and "block" the allergic response. Current opinion is against this, partly because the increase in IgG levels follows rather than precedes the onset of clinical benefit and partly because many mast cells are on the mucosal surfaces and therefore meet allergen before antibodies can interpose themselves. Moreover, there is a poor correlation between the amount of allergen-specific IgG and clinical protection. In most studies the IgG level correlates better with the dose of allergen that has been given rather than with the degree of protection achieved. That said, there has been a recent resurgence of interest in a possible inhibitory role of specific IgG antibodies in grass pollen immunotherapy.[4] In particular, the time course of this effect raises the possibility of specific IgG antibodies interfering with IgE-dependent cytokine secretion from mast cells or facilitated antigen presentation to T cells.

SIT also induces changes in allergen-specific T-cell responses. In nasal and skin allergen challenge models, successful SIT is accompanied by a reduction in T-cell and eosinophil recruitment in response to allergen. In parallel, there is a shift in the balance of T_H1 and T_H2 cytokine expression in the allergen-challenged site. T_H2 cytokine expression is not affected, but there is an increased proportion of T cells expressing the T_H1 cytokines IL-2, IFN-γ, and IL-12.[5-7] After venom SIT, there is induction of allergen-specific $CD4^+$ regulatory T cells that express CD25, forkhead box protein 3, and IL-10, as well as a shift in T_H1/T_H2 balance.[8,9] Similar findings have also been reported after SIT with inhalant allergens.[10] IL-10 has a complex series of actions on the immune response, including downregulation of T cells and induction of allergen-specific IgG4 antibodies, which probably explains the IgG4 response to SIT. If the IL-10 effect on T cells is what matters, then the IgG4 response should perhaps be viewed as a surrogate marker of IL-10 induction rather than the beneficial mechanism of SIT.[11] Overall, it is clear that SIT has a modulatory effect on allergen-specific T cells, and it seems that this is why clinical and late-phase responses are attenuated without suppression of allergen-specific antibody levels or immediate allergic responses.

TABLE I. Possible mechanisms of immunotherapy

Reduction in specific IgE levels (long-term)
Induction of IgG (blocking) antibodies
Reduced recruitment of effector cells
Altered T-cell cytokine balance (shift to T_H1 from T_H2)
T-cell anergy
Induction of regulatory T cells

CLINICAL INDICATIONS

SIT for venom hypersensitivity

Anaphylaxis to Hymenoptera venom is relatively rare but can be fatal. Venom-specific IgE antibodies are found in 30% to 40% of all adults for a few months after a sting, but these usually disappear in a few months. This response is related to the total serum IgE level and the patient's IgE response to inhalant allergens. Some unlucky subjects react more vigorously with high concentrations of venom-specific antibodies, which can persist for many years without further exposure to stings. This group of patients are at risk of anaphylaxis to subsequent stings, and a small number die from anaphylaxis each year. Precise figures are hard to come by, but a figure of at least 40 deaths per year in the United States has been cited. Additional sting-related deaths may have occured in persons reported to have died of unknown cause.[12]

The purpose of venom immunotherapy (VIT) is 2-fold: to reduce the risk of fatality and to improve the patient's quality of life by allowing him or her to go out and work or play without worrying about the possibility of a serious allergic reaction. Given the relatively small number of fatalities, the main effect of VIT is on a person's quality of life. The decision to proceed with VIT is based on a 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 compared with 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 a previous systemic reaction is between 30% and 70%. In general, children are less at risk of repeated systemic reactions, as are those with a history of milder reactions. With time, the risk of a systemic reaction decreases: by 10 years after a previous systemic response, the risk is about 15% compared with the general population's risk of 2% to 3%. Occupational and geographic factors that might affect the likelihood of future stings should also be considered. Bee stings are much more common in beekeepers, their families, and their neighbors. For most persons, wasp stings are sporadic, but they are an occupational hazard for bakers, greengrocers, gardeners, tree surgeons, for example. Other factors to consider are the potential risks of emergency treatment with epinephrine and the various medical contraindications to SIT (see below).

Desensitization with venom accelerates the rate at which the risk decreases and rapidly provides protection against field and laboratory stings. After completing VIT, there is a residual risk of systemic reactions of approximately 10%, but when reactions do occur to stings after VIT, they are typically mild. Patients who

receive VIT should be supplied with antiallergic medication for use in the event of a sting during or after therapy. Some allergists recommend providing injectable epinephrine 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 all forms of SIT, it is important to select patients appropriately. The allergic basis of the rhinitis should be carefully assessed based on both history and skin or blood test results, and other causes of nasal symptoms should be excluded. Direct challenge tests to assess nasal sensitivity to allergen are not used in routine clinical practice but might be useful for assessing effectiveness in clinical trials. The most difficult group to assess are patients with persistent nonseasonal rhinitis, especially those who have small positive skin test responses to house dust mite or other perennial allergens. In this group it can be extremely difficult to determine whether the patient's symptoms are truly due to allergy or whether they have nonallergic rhinitis and just happen to be sensitized to an allergen that is not clinically relevant. This difficulty in determining clinical relevance contributes to the reported lower degree of efficacy in SIT trials with perennial allergens compared with SIT for seasonal allergies.

The effectiveness of SIT in patients with intermittent (seasonal) allergic rhinitis has been confirmed in many trials with grass, ragweed, and birch pollen extracts.[14] Importantly, SIT has been shown to be effective even in patients with severe seasonal rhinitis caused by grass pollen that is resistant to conventional drug therapy.[15] Importantly, this study showed that patients with multiple allergic sensitizations responded at least as well as those who were monosensitized to grass pollen.

The benefits of 1 year's treatment wear off quickly,[16] but there are good data showing that 3 years' therapy provides lasting benefit.[17] Less well-controlled data show that the effects of SIT can persist for many years after discontinuing therapy.[18] This contrasts with conventional drugs, the effects of which wear off very soon after discontinuing therapy. The benefits of SIT for perennial rhinitis are less than those for seasonal rhinitis. In part, this reflects the difficulty in determining the extent to which allergy is responsible for perennial symptoms. Sensitization to house dust mite is common and does not always cause symptoms. Conversely, there are other causes of perennial rhinitis, including vasomotor instability, infection, and aspirin sensitivity. Nevertheless, clinical trials have shown a definite benefit in appropriately selected subjects. Clearer evidence has been obtained in patients with rhinitis caused by pet allergy. Several studies have shown a marked improvement in tolerance of cat exposure after SIT, which was confirmed both on challenge tests and simulated natural exposure.[19]

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 minority of patients have suboptimal control of their symptoms.[20] Some patients with rhinitis experience nosebleeds from intranasal steroids or excessive 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 (eg, the United Kingdom) 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.[21,22]

Current drug therapies for asthma aim to suppress airways inflammation and relieve bronchospasm. None of these treatments are curative, and asthma recurs rapidly on ceasing treatment. Allergen avoidance helps in some patients with allergic asthma, but although extreme forms of allergen avoidance (eg, admission to the hospital and sending children to holiday homes at altitude) can improve asthma control, there is only limited evidence for benefit with the degree of allergen avoidance that can be achieved in suburban homes. There is thus the 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 toward 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 65 years. The results of these studies have often been difficult to interpret, either because poor-quality allergen extracts were used or because of poor study design. Many trials were not placebo controlled; they were either open or single blind, and in most cases, only small numbers of patients were treated. A recently updated meta-analysis[22] identified 75 articles published between 1954 and 2001. Thirty-six of these were for mite allergy, 20 for pollen allergy, 10 for animal dander allergy, 2 for mold allergy, and 1 for latex allergy, and 6 used combinations of allergens. Concealment of allocation was clearly adequate in only 15 trials. A wide variety of different measurements were made, which makes it difficult to comment on the overall effectiveness of SIT. Symptom scores improved in the treated groups; it was necessary to treat 4 patients to prevent 1 from experiencing symptom exacerbation and to treat 5 patients to prevent 1 from needing an increase in medication use. SIT reduced the airways response to inhalation of specific allergen and also improved nonspecific bronchial reactivity.

Three double-blind, placebo-controlled studies have found that SIT has a beneficial effect in patients with grass pollen–induced asthma, as assessed by a reduction in asthma symptom and treatment scores. Active treatment led to a 60% to 75% reduction in symptom scores compared with those seen in placebo-treated patients. An important 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.[23] In addition, the active group required much less antiasthma medication. However, the parallel economic analysis indicated that the cost savings in asthma drugs was 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 hyperresponsiveness, despite the clear delay in 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 nonspecific bronchial reactivity after SIT for cat allergy (measured by using inhalation challenges with cat extract and histamine, respectively).[24]

The main drawback in using SIT to treat asthma is the risk of serious adverse reactions. The vast majority of fatal reactions to SIT have occurred in patients with asthma, and although asthma is not an absolute contraindication, it is clear that patients with unstable asthma should not be offered SIT, and caution should be exercised in anyone with an increased level of asthma symptoms or transiently reduced peak flow rates.

Comparison of SIT with other types of treatment for asthma

The majority of clinical trials of SIT for patients with asthma have compared SIT either with untreated historical control subjects or with a matched placebo-treated group. To date, the effectiveness of SIT in patients with asthma has rarely been compared with conventional management (avoidance measures and inhaled or oral antiasthma 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.[25] There were some significant flaws in the design of this study, and further work of this type is urgently needed.

Effects on natural history of allergic disease

Children often start with a limited range of allergic sensitivities and progress over time to have IgE against a wider range of inhaled allergens. Treatment with SIT might limit this tendency to acquire new sensitizations,[26] although the clinical benefit of this preventive effect is not clear. A proportion of patients with allergic rhinitis develop asthma each year. This annual rate of progression has been estimated at 5% in college students,[27] but this is perhaps surprisingly an area of considerable ignorance. A number of long-term epidemiologic studies are now in progress under the auspices of the International Study of Asthma and Allergies in Childhood, and these should eventually shed light on the rate of progression at different ages and the extent of regional and international variation. It has been suggested that SIT might modify the natural history of asthma in children who are known to be atopic but have not yet developed asthma. Only limited data are available to support this proposition. In the key study a group of 205 children aged 6 to 14 years without previously diagnosed asthma were treated with SIT for birch or grass pollen allergy in an open randomized design. Three years after completing treatment, 45% of the untreated group had asthma, whereas only 26% of the treated group had asthma. These results have been sustained out to 7 years after completing therapy. Thus 4 children had to be treated to prevent 1 case of asthma, which makes this an extremely effective therapy.[28] SIT might also modify the progression of established asthma. An early open study with uncharacterized mixed allergen extracts supported this view, with about 70% of treated children losing their asthma after 4 years' therapy compared with about 19% of untreated control subjects, a result that was sustained up to the age of 16 years. The proportion of children whose asthma was severe at age 16 years was also much lower in the treated group.[29] By modern standards, this study was not well designed, and it needs repeating with modern SIT extracts in an up-to-date trial design.

In contrast, there is no current evidence that SIT influences the evolution of established asthma in adults. 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.[30]

Thus SIT is a valid but controversial treatment for asthma. Although 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. To assess this properly would require comparisons of best current SIT versus best current drug therapy, with robust end points 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 asthmatic subjects, but there is increasing evidence that SIT is beneficial in patients with 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 patients with mild-to-moderate childhood asthma and also in patients with atopic disease who have not yet had asthma but are at high risk of progression to asthma.

Safety of SIT

The most obvious risk of SIT is that of provoking a systemic allergic reaction. In the United Kingdom between 1957 and 1986, 26 fatal reactions caused by SIT were reported to the Committee on Safety of Medicines.[31] The indication for SIT was documented in 17 of the fatal cases, 16 of whom were in patients receiving SIT to treat their asthma. Similarly, in the American Academy of Allergy, Asthma & Immunology inquiry into SIT-associated deaths, asthma appeared to be the cause of death in most of the fatal cases.[32,33] In those cases in which asthma was not cited as a contributory factor, asthma status was not documented, whereas bronchospasm was a feature of the clinical course of the fatal 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%. The central issue in using safety as an end point is that we have to accept 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. However, where possible, we should take steps to minimize the risks.

Separately, there is some concern about the use of immunomodulatory treatments in patients with autoimmune disorders, immunodeficiency syndromes, or malignant disease. Although there is no hard evidence that SIT is actually harmful to these patients, some clinicians feel uncomfortable about manipulating the immune system in such patients, not least because of the risk that spontaneous and unrelated variations in the autoimmune

disorder or cancer might be blamed on SIT. However, provided the risks and benefits are weighed and discussed with the patient, SIT can be administered where the risk/benefit ratio is considered to be in favor of treatment. Other medical contraindications to SIT include the coexistence of significant cardiac disease that might be exacerbated by any adverse reactions to SIT. β-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 the epinephrine that might be needed to treat adverse reactions to SIT. Where the indication for SIT is strong, alternatives to β-blockers should be used so that the SIT can be given safely. Some clinics advise avoiding angiotensin-converting enzyme inhibitors because they can accentuate angioedema (angiotensin receptor antagonists [sartans] do not share this property).

Alternative forms of immunotherapy

Alternative allergy practice covers 3 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 that are not conventionally considered to involve allergic mechanisms. Alternative immunotherapy regimens fall into the second of these categories, but the other 2 areas fall outside the scope of this review.

Unconventional forms of immunotherapy include the use of topical immunotherapy, enzyme-potentiated desensitization (EPD), and homeopathic desensitization.

Topical immunotherapy. High-dose topical immunotherapy regimens were used in the first half of the 20th century but subsequently fell into disrepute. The last 20 years have seen a revival of interest in sublingual immunotherapy (SLIT). The precise mechanisms by which sublingual SIT works remain unclear. 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 toward a T_H1 profile and away from the pro-IgE T_H2 profile. It is less clear whether this mechanism can suppress established allergic responses. In contrast, the immunologic response to SLIT in human studies has been relatively modest. Some changes have been found in skin sensitivity, but most studies have not found any change in systemic parameters, such as specific IgE, specific IgG, or T-cell cytokine balance.

A body of evidence has accumulated from well-conducted clinical trials indicating that SLIT can be effective, with up to 30% to 40% reductions in symptom scores and rescue medication use in patients with seasonal allergic rhinitis.[34] Treatment regimens typically involve a rapid build-up phase followed by treatment given either daily or 3 times per week with rapidly dissolving tablets containing allergen extracts. Some preparations are supplied in liquid form, with a calibrated dropper. A recent meta-analysis of SLIT found 22 studies in which 979 patients received active therapy.[34] Although many of these studies were small and inconclusive, the combined results indicate that SLIT is indeed effective, with an estimated power of about two thirds that seen in comparable studies of injected SIT. Local side effects were common but well tolerated.

In the grass pollen tablet trials about half the patients experienced some local irritation with the first dose. This was minor and generally did not require a reduction in subsequent doses. About half of those with initial side effects had lost these by the eighth day of treatment; only 1 in 25 of all patients had continuing local side effects after 3 months treatment.[35] Systemic side effects were relatively rare, and none of the side effects were judged to be life-threatening. For perennial allergens, less trials data are available,[36] and only limited data are available in children, although the most recent studies have been encouraging.[37,38] Other forms of topical immunotherapy (oral and nasal) have limited efficacy but are associated with high levels of side effects.

SLIT is now being used routinely in some parts of Europe (especially Italy and France), but often the doses and regimens being prescribed are different from those used in the clinical trials. As performed in the published trials, SLIT involves giving 20 to 400 times the total dose that would be given in a course of injected SIT. There is no evidence that giving smaller doses sublingually has any clinical effect. Overall, SLIT is likely to widen the scope of SIT and bring in additional prescribers. As with all forms of immunotherapy, patient selection will be the key to ensuring that therapy is targeted to those who are likely to benefit from it.

Some areas of uncertainty remain. For example, the optimum duration and durability of therapy have not been defined. Recent clinical trials have confirmed that the benefits of SLIT persist for the first year after discontinuing treatment, but if they do persist, for how long do they persist? Based on experience with injected SIT, manufacturers recommend that SLIT should be continued for 3 years, although most clinical trials were short-term (6-12 months). For seasonal allergens, most open-label use in clinical practice has been intermittent, starting 2 to 3 months before the season and stopping at the end of the season. However, the manufacturer of the only licensed product recommends starting 4 months before the first grass pollen season and continuing throughout the year for 3 years. This has major implications for direct costs and cost-effectiveness,[39] and some supporting data would be welcome.

The relative efficacy of SLIT and injected SIT has not been determined. The only published comparative studies were far too small to produce meaningful results.[40,41] Based on the effect size seen in the meta-analyses,[14,34] it seems likely that SLIT has between 60% and 100% of the efficacy of injected SIT, although it is difficult to make a true comparison.

EPD. In EPD very small doses of allergens are given together with the enzyme β-glucuronidase. The allergen doses are approximately 0.1% of the doses used in conventional SIT, and side effects are apparently not encountered. The theory behind EPD is that the β-glucuronidase enables the allergen to gain access to the immune system more efficiently than is possible with conventional SIT. No convincing evidence has been published to support the efficacy of EPD.

Homeopathic desensitization. A detailed discussion of the principles underlying homeopathy lies outside the scope of this chapter. However, homeopathy espouses the concept that diseases can be treated with very small doses of substances that cause similar symptoms. Some homeopathic remedies are mimics of the disorder, whereas others use the actual material that triggers the disorder. Thus homeopathic remedies for hay fever bear some superficial similarity to SIT. A systematic review of homeopathy has concluded that homeopathy did appear to offer some benefit in patients with hay fever and cited trials of homeopathy in hay fever as an example of good practice in homeopathic research.[42] However, a more recent, carefully controlled study of homoeopathy for house dust mite allergy found no evidence of any benefit in patients with asthma.[43]

TABLE II. Possible new technologies for immunotherapy

Recombinant allergens
Hypoallergenic allergens (bioengineered recombinant molecules)
T-cell peptide vaccines
T_H1 immunostimulants (eg, mycobacteria and CpG)
Allergen-immunostimulant complexes
Anti-IgE

FUTURE DIRECTIONS

There is scope to improve conventional SIT (Table II). Possible avenues include the use of recombinant allergens, which would improve standardization of allergen vaccines and might allow fine tuning of vaccines for patients with unusual patterns of reactivity. Most allergic patients react to the same components of an allergen extract, the so-called major allergens, which are defined as those allergens recognized by more than 50% of sera from a pool of patients with clinically significant allergy to the material in question. However, not all patients recognize all major allergens, and some patients only recognize allergens that are not recognized by the majority of allergic patient sera. This latter group might not respond to standard extracts but might be better treated with a combination of allergens to which they are sensitive. Now that recombinant allergens for SIT are available, the range of sensitivities can be better characterized, and this might lead to patient-tailored vaccine products. Thus far, clinical trials have confirmed the efficacy of recombinant allergen cocktails but have not yet shown superiority to conventional vaccines.[44]

Novel forms of allergenic molecules can be created; for example, a recombinant trimer consisting of 3 covalently linked copies of the major birch pollen allergen Bet v 1 has been made. This trimer is much less allergenic, even though it contains the same B-cell and T-cell epitopes as the native molecule and induces T_H1 cytokine release and IgG antibodies analogous to the antibody response to standard SIT.[45] Folding variants and other modifications of the physical structure might also improve the safety of SIT.[46]

Because the epitopes recognized by IgE molecules are usually 3-dimensional, whereas T-cell epitopes are short linear peptide fragments of the antigen, it should be possible to use peptide fragments of allergens to modulate T cells without risking anaphylaxis. Two distinct approaches have been tested. Either large doses of natural sequence peptides are given, deceiving the T cell into high-dose tolerance,[47] or else an altered peptide ligand can be given. Both approaches require consideration of the MHC type of the subject undergoing treatment. By means of sequential alteration of *Dermatophagoides pteronyssinus* peptides, it is possible to suppress proliferation of T-cell clones recognizing native *D pteronyssinus* peptides, as well as suppressing their expression of CD40 ligand and their production of IL-4, IL-5, and IFN-γ. These anergic T cells do not provide help for B cells in class switching to IgE, and importantly, this anergy cannot be reversed by providing exogenous IL-4.[48]

In an animal model intranasal application of genetically produced hypoallergenic fragments of Bet v 1 produced mucosal tolerance, with significant reduction of IgE and IgG1 antibody responses, as well as reduced cytokine production *in vitro* (IL-5, IFN-γ, and IL-10). These reduced immunologic responses were accompanied by inhibition of the cutaneous and airway responses that were seen with the complete Bet v 1 allergen. The mechanisms of immunosuppression seemed to be different for the allergen fragments and the whole molecule in that tolerance induced with the whole Bet v 1 molecule was transferable with spleen cells, whereas that induced by the fragments was not.[49]

From epidemiologic and experimental studies, we know that vaccination with mycobacteria has antiallergic properties. In Japan early vaccination with BCG was associated with a substantial reduction in the risk of allergy,[50] although similar associations were not evident in Sweden.[51] In an animal model it has been shown that administration of BCG before or during sensitization to ovalbumin reduces the degree of airway eosinophilia that follows subsequent challenge with ovalbumin. This effect is not mediated through any direct effect on IgE production or blood eosinophil numbers but is mediated through IFN-γ and can be reversed by exogenous IL-5.[52]

Two new approaches using DNA vaccines are also undergoing serious consideration. The first of these is a general approach, using CpG oligodeoxynucleotides that mimic bacterial DNA and stimulate T_H1-type cytokine responses. In a murine model of asthma, preadministration of CpG oligodeoxynucleotides prevented both airways eosinophilia and bronchial hyperresponsiveness.[53] Moreover, these effects were sustained for at least 6 weeks after CpG oligodeoxynucleotide administration.[54] An alternative approach is to couple CpG oligodeoxynucleotides to the allergenic protein, which enhances immunogenicity in terms of eliciting a T_H1-type response to the allergen but reduces its allergenicity[55] and stimulates T_H1 cytokine expression in cultured human PBMCs.[56] Initial clinical trials confirmed that the hybrid vaccine elicits a T_H1-pattern response,[57] but subsequent trials have been inconclusive. A contrasting approach is to use allergen-specific naked DNA sequences as vaccines. This technology is still in its infancy, but preliminary data suggest that administering naked DNA leads to production of allergens from within the airways epithelial cells.[58,59] Because of the different handling pathways for endogenous and exogenous allergens, it seems that the endogenously produced allergen elicits a T_H1-type response, and if this can be reproduced in allergic human subjects, it is hoped that this might overcome the existing T_H2-pattern response and eliminate the allergy. However, the potential for generating a powerful T_H1-type response to ubiquitous agents means that this approach will require careful evaluation in animal models before it can be pursued in human subjects.

CONCLUSIONS

SIT has been used for more than a century and is clinically effective in patients with rhinitis or asthma whose symptoms are clearly driven by allergic triggers. Perhaps surprisingly, we are still unsure exactly how SIT works, but we do know that SIT 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. Future directions in SIT will include the development of better standardized vaccines and the use of recombinant allergens, both of which should improve the safety profile of SIT. In parallel, the development of allergen-independent immunomodulatory therapies might allow more general approaches to be developed, which would be particularly advantageous for those patients who are sensitized to multiple allergens.

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